Abdominal and Pelvic Pain

Acute Cystitis Increases Sensory Neuron Excitability in Intact Dorsal Root Ganglion

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Urologic chronic pelvic pain (UCPP), sometimes a result of cystitis, is often accompanied by somatic pain that is poorly understood and underdiagnosed. Uninjured, bystander neurons in dorsal root ganglia (DRG) are known to contribute to neuropathic pain. However, mechanisms underlying somatic "referred pain" remains unclear. Mirroring lower limb hypersensitivity of UCPP patients, our cystitis mouse model produces secondary mechanical hypersensitivity in hind paw skin. We conducted ex vivo Ca2+ imaging studies to test the hypothesis that cystitis increases neural activity in bladder- and paw- innervating DRG. Dual tracer studies confirmed DRGs that contain both bladder (L5-L6) and paw afferents (L3-L6). Female Snap25-GCaMP6s-D mice were randomly assigned to receive urinary catheter installation of acrolein (cystitis, n = 6) or saline (control, n = 8). Behavioral assays confirmed voiding dysfunction lasted at least 48 hours after cystitis but paw sensitivity varied. At 48-hours, whole L3-L6 DRGs were acutely dissected. Changes in neuron GFP fluorescence were measured after depolarizing stimuli (30mM KCl) and peak amplitudes were compared using Mann-Whitney tests. After cystitis, neurons exhibited larger amplitude responses in L5 ($p<0.0001$) and L6 DRG ($p<0.0001$), suggesting increased excitability in bladder-innervating DRG. Notably, with little to no bladder afferents but abundant paw afferents, L3 ($p<0.0001$) and L4 DRG ($p<0.0001$) also exhibited larger amplitude responses after cystitis, suggesting increased excitability of bystander neurons that do not innervate the bladder. Ongoing pharmacologic and gene expression experiments will help elaborate on specific molecular contributors and retrograde tracing will investigate paw afferent hyperexcitability after cystitis.

Central Amygdala Hemisphere-Specific Calcitonin Gene Related Peptide Receptor Excitability After Bladder Injury

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The central nucleus of the amygdala (CeA) is known to be involved in the emotional-affective component of pain. The spino-parabrachio pathway that carries direct nociceptive information equally projects to the right and left CeA. However, the right CeA is known to dominate pain processing compared to the left CeA. In the cyclophosphamide-induced visceral-pain model, we showed that activating the right CGRP (calcitonin gene related peptide) releasing projections to the CeA increased pain-related hypersensitivity. Conversely, inactivating the left side recapitulated hypersensitivity, while activating it reduced it. This opposing action of CGRP on CeA may be because of injury-induced differential excitability in the left and right CeA. We hypothesized that, the right CeA CGRPR+ (CGRP-receptor) neurons exhibit higher excitability after bladder sensitization. Conversely, the left side exhibit lower excitability compared to the control group. We report that, post-injury, the left CGRPR+ neurons exhibited a higher rheobase compared to the control group, indicating reduced excitability. In terms of the firing frequency, interestingly, the left CeA responded with increased firing to a smaller current injection.

However, at higher current injections, a current block was introduced, resulting in a complete loss of firing. The right side did not show any change in excitability after injury compared to controls. The results suggest a hemisphere-specific neuronal function in pain-processing and further emphasizes the presence of hemispheric-specific response patterns in the context of pain and nociception.

Complex Spinal Mechanisms Underlying Stress-Induced Bladder Hypersensitivity in Hemopexin Depleted Mice

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Urologic Chronic Pelvic Pain Syndrome (UCPPS) is characterized by chronic urologic pain, often accompanied by increased urinary frequency and urgency. Prior studies link stress to UCPPS development, but the mechanisms remain poorly understood. This study investigates the role of hemopexin (Hpx) in stress-induced bladder hypersensitivity. Adult female Hpx knockout (KO) and wild-type (WT) mice were exposed to acute water avoidance stress (aWAS) for 1 hour. 24 hours later, bladder nociception was assessed via visceromotor response to graded urinary bladder distensions (UBDs; n=12). A separate cohort of mice underwent in vivo spinal electrophysiology during graded UBD (nmice=8-12; nneurons=32-50). A three-way ANOVA revealed that aWAS significantly increased visceromotor responses in Hpx KO mice ($p<.05$), but not in WT mice. Similar analysis of spinal electrophysiology revealed reduced evoked activity of wide dynamic range (WDR) neurons in both genotypes after aWAS ($p<.001$). Evoked nociceptive-specific (NS) neuronal activity was highest in WT controls compared to other groups ($p<.01$). Hpx KO mice exposed to aWAS showed more Type II neurons (not inhibited by heterotopic noxious conditioning stimulus; HNCS) than Type I neurons (inhibited by HNCS; $p<.05$). These data demonstrate that aWAS increased bladder hypersensitivity in Hpx KO animals only, possibly due to the phenotypic switch in the quantity of Type I to Type II neurons. However, other electrophysiological measures suggest that stress-induced analgesia is also present, highlighting the complexity of spinal neuronal recruitment during noxious stimuli. Further studies will examine the activity of supraspinal structures to better understand the impact of Hpx depletion on bladder sensitivity.

Dysmenorrhea And Chronic Pain Risk: Evidence From A Large-Scale Retrospective Electronic Medical Record Database

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Persistent, severe dysmenorrhea is hypothesized to induce central sensitization, potentially precipitating the development of chronic pain. To evaluate whether sleep and inflammatory mechanisms are also disrupted by dysmenorrhea, we conducted a retrospective analysis of new-onset conditions within five years of diagnosis of dysmenorrhea using TriNetX, a large-scale Electronic Health Record (EHR) dataset. Dysmenorrhea was identified using the ICD-10 code N94.6. Eligibility criteria included at least two gynecological exams and two healthcare visits to

ensure adequate clinical records. Exclusion criteria encompassed individuals with fibroids, endometriosis, polycystic ovarian syndrome, leiomyomas, hysterectomies, BMI outside 18.5-24.9 kg/m2, or nicotine dependence. Propensity score matching was applied to adjust for age, race, pregnancy status, and socioeconomic factors. Both cohorts (n=180,588 each) had a mean age of 22.1 (SD 7.3) years, and 16.7% identified as Black. Dysmenorrhea was significantly associated with increased odds of pain conditions, including chronic pelvic pain (OR [95 CI] = 2.2 [2.1-2.2]), irritable bowel syndrome (1.9 [1.8-2.0]), and interstitial cystitis (2.2 [1.8-2.6]). Additionally, patients with dysmenorrhea demonstrated higher risks of sleep dysfunction, such as insomnia (1.8 [1.7-1.9]) and sleep apnea (1.86 [1.7-2.0]). Notably, the dysmenorrhea cohort exhibited a 4% mean lower white blood cell count but elevated eosinophil (13%) and basophil (12%) counts ($p < 0.001$). Findings suggest that dysmenorrhea involves broad impairments in homeostasis, including sleep and inflammatory dysfunction, which may contribute to an elevated risk of chronic pain. These findings highlight the need to consider dysmenorrhea within a broader systemic context beyond reproductive health.

Hormonal Mechanisms of Endometriosis Pain in Mouse and Human

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Endometriosis is a chronic inflammatory condition affecting 10% of individuals with a uterus, characterized by severe, persistent pelvic pain. Within the peritoneum, tissue lesions form consisting of endometrial cells, immune cells, and peripheral nerve axons. Treatments include the suppression of cycling sex hormones or lesion excision surgery. Both are successful in some patients but have several side effects, and, following the surgery, lesions often return along with the corresponding pelvic pain. Since endometriosis is an estrogen-dependent disease and because lesions are densely innervated, we hypothesized that increased hormone signaling in lesions sensitizes the innervating sensory neurons, leading to pelvic pain. To investigate this, we collected patient-reported outcomes and conducted sensory testing before surgery. Analysis of patient lesions revealed that the hormonal microenvironment, and, in particular estrogen signaling, is distinct from nearby non-lesion tissue in the peritoneal cavity. To further explore nociceptive mechanisms, we replicated a mouse model of endometriosis which formed peritoneal lesions that are histologically similar to those observed in humans. Also, we observed that mice exhibited increased abdominal mechanical and spontaneous pain-like behaviors compared to controls. Retrograde tracer injection into the lesion revealed dorsal root ganglion (DRG) neuron labeling, many of which co-expressed estrogen receptor beta (ERβ). Further, we found that neurons innervating the lesions were hyperexcitable compared to those innervating non-lesion areas. These findings highlight a potential interaction between local hormonal signaling in endometriosis lesions and sensory neuron sensitization, offering new insights into the mechanisms that drive pain in this condition.

TRPV1-expressing Primary Afferent Neurons Drive Pelvic Tactile Allodynia in

Endometriosis- and Uterine VEGF-associated Mouse Models of Chronic Pelvic Pain
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Endometriosis (EM) impacts roughly 10% of reproductive-age women globally. EM lesions are infiltrated with mast cells (MCs) and are densely innervated. We used a non-invasive mouse model of EM to test the hypothesis that MCs and primary afferent neuron innervation contribute to EM-associated pelvic pain. C57BL/6J donor mice (6 weeks old) received a subcutaneous injection of estradiol benzoate (10µg), and 4 days later, each uterine horn was excised and placed in Hank's Balanced Salt Solution (HBSS) and minced. Recipient mice received an intraperitoneal injection of either HBSS (500µl; "Shams") or HBSS+ donor mice minced uterine horn (500µl; "EM mice"). Our results revealed that VEGF-expressing MCs are adjacent to CGRP+ afferents in the uterine tissue of EM mice but not Sham controls. Next, we suprapubically applied von Frey filaments to assess mechanical hypersensitivity after ablation of TRPV1-expressing sensory neurons with intrathecal (i.t.) capsaicin (CAP; 1µg) or resiniferatoxin (RTX; 25ng). In Shams, neither vehicle, CAP, nor RTX changed mechanical thresholds. In EM mice, CAP and RTX but not saline reversed hypersensitivity ($p<0.05$). Follow-up studies demonstrated that intrauterine VEGF dose-dependently induced pelvic tactile allodynia in non-EM mice; thus, we investigated the effect of afferent ablation in this model. In mice with VEGF-induced pelvic tactile allodynia, RTX but not vehicle reversed VEGF-induced hypersensitivity ($p<0.05$). We conclude that: 1) VEGF-expressing MCs are adjacent to peptidergic afferents in EM, and 2) TRPV1-expressing primary afferent neurons contribute to EM-associated and VEGF-induced pelvic tactile allodynia.

Nucleus Tractus Solitarii Response to taVNS in Patients with Functional Dyspepsia is Associated with Abdominal Pain: A 7T Pilot Study
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Function dyspepsia (FD) is one of the most common gastrointestinal disorders in the United States, characterized by chronic epigastric symptoms, including pain. Evidence shows that FD is a disorder of gut-brain interaction: low gastric motility was associated with abnormal connectivity of nucleus tractus solitarii (NTS) in the brainstem (Sclocco et al. 2022). We previously found that transcutaneous auricular vagus nerve stimulation (taVNS), a promising intervention for FD, elicited the strongest NTS activation at 100Hz in healthy individuals (Sclocco et al. 2020). Whether taVNS also strongly activates NTS at 100Hz in patients with FD is unknown. Here, we investigated brainstem response to respiratory-gated taVNS (delivered at 2Hz, 10Hz, 25Hz or 100Hz) in patients with FD, and sought to link response to upper abdominal pain. Eight patients with FD participated in the study (38 ± 17 years old; 7:1 (F:M)). They rated their upper abdominal pain on the Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index. Ultrahigh field (7T) fMRI was acquired with a Siemens Terra scanner. Brainstem fMRI response was assessed with FEAT (FSL), using non-parametric permutation analysis. On average, patients reported mild upper abdominal pain (1.75 ± 1.4, 0-4, on a severity scale of 5) over 2-weeks prior to the scan. Left (ipsilateral) NTS was most activated at 100Hz compared to

sham, and activation was negatively correlated with pain ratings (r= -0.64, p=0.09). NTS response may prove to be a longitudinal or predictive biomarker for therapeutic response to taVNS in FD.

Uterine-Innervating Neuron Sensitization in a Mouse Model of Endometriosis Pain
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Chronic pain is one of the cardinal symptoms of endometriosis, a condition that affects at least 10% of individuals with a uterus. Although the anatomical and molecular basis of endometriosis pain is debated, hysterectomy alleviates pain in a subset of patients. Thus, we hypothesized that uterine-innervating neurons may be preferentially sensitized to noxious stimuli in individuals with endometriosis. To test this hypothesis, we induced endometriosis in C57BL/6 wildtype mice via intraperitoneal injection of homogenized uterine tissue from donor mice. We confirmed the development of visceral mechanical allodynia in endometriosis mice through abdominal von Frey testing and quantification of spontaneous pain behaviors. To investigate changes in uterine-innervating neuronal activity in endometriosis, we injected the uterus of both sham and endometriosis mice with fluorescently tagged cholera toxin subunit B, a neuroanatomical tracer. DRG neurons from levels T11-S2 were cultured from all mice and back-labeled uterine-innervating neurons were quantified at each spinal level. Calcium flux in response to extracellular application of prostaglandin E2 (PGE2), a proinflammatory compound that is elevated in the peritoneal fluid of individuals with endometriosis, was measured in both uterine-innervating and non-uterine-innervating neurons. Histological analysis of mouse uterine tissue was also performed to visualize disease-related changes in uterine innervation. Taken together, these experiments are the first to study changes in anatomical and functional properties of uterine-innervating neurons in mice with endometriosis.

Validation of A Non-Invasive Method to Monitoring of Uterine Hypoxemia to Understand Pain in Mechanisms in Dysmenorrhea
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Dysmenorrhea causes severe pain and significantly impacts the quality of life for many individuals worldwide. It is widely hypothesized that transient uterine hypoxemia resulting from uterine contractions underlies menstrual pain; however, prior research has been limited by invasive methods that may provoke contractions. To address this gap, we developed a novel magnetic resonance imaging (MRI)-based approach to monitor uterine oxygenation non-invasively. Blood oxygen level-dependent echo planar imaging (EPI-BOLD) can be used to evaluate transient hypoxemia based on the magnetic properties of hemoglobin, the oxygen-carrying molecule in the blood, depending on if it's oxygenated (oxyhemoglobin) or deoxygenated (deoxyhemoglobin). We validated the ability to measure uterine oxygenation using EPI-BOLD sequences in 10 participants during a 2-minute inhalation of 100% oxygen (10 L/min). This resulted in a 3.6 +- 0.6% increase in myometrial signal intensity ($p < 0.001$). During

menstruation, we captured 10-minute EPI-BOLD sequences for individuals with dysmenorrhea (n = 15) and pain-free controls (n = 10). Transient signal intensity reductions (>=5% from baseline, lasting >=20 seconds), representing deoxygenation during contractions, were observed in 9/12 participants with dysmenorrhea but not in controls. After naproxen administration, only 4 participants continued to experience these reductions in signal intensity, with 2 of these 4 reporting significant residual pain despite treatment. Across all participants, uterine hypoxemia correlated with unresolved pain ($r2 = 0.46$, $p < 0.001$). These preliminary findings suggest EPI-BOLD can measure transient uterine oxygenation changes, linking menstrual pain to transient uterine hypoxemia during contractions, although further extensive studies are needed. NIH (R01HD098193).

Menstrual Pain, Psychological Factors and Pain Interference in Adolescents Early Post-Menarche

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Pubertal maturation is associated with increased pain conditions in adolescence. Moreover, some features of pubertal development such as early menarche are associated with more severe chronic pain in adulthood. Although the connection is not well understood, menarche has been associated with increased sleep deficiencies and psychological distress in female adolescents. We aimed to determine the associations between menstrual pain intensity, pain interference, psychological distress, and sleep duration early after menarche, when pain and behavioral patterns may become established lifelong. From a larger cohort study on menarche, 58 females (age M=12.6 years, SD=1.0; 78.6% White) were recruited pre-menarche and followed longitudinally. At 3-9 months post-menarche, they reported on menstrual pain intensity (0-10), pain interference, anxiety, and depression (PROMIS@), and completed a 7-day actigraphy sleep assessment. Preliminary findings showed that adolescents had mild menstrual pain (M=3.8, SD=2.4). Within the sample, 26.3% had elevated scores for anxiety, 12.3% for depression, and 38.5% for pain interference (T-scores > 60). Nightly sleep duration averaged 7 hours, 27 minutes (SD=50). Multivariate regression analyses demonstrated that anxiety was significantly associated with greater pain interference ($b=0.49$, $p<.001$), but not menstrual pain or sleep duration ($F(3, 53)=7.52$, $p<.005$), explaining 25.9% of the variance. Similarly, depressive symptoms were also associated with greater pain interference ($b=0.55$, $p<.001$), but not menstrual pain and sleep duration ($F(3, 53)=7.52$, $p<.001$). Findings revealed that anxiety and depression were strongly associated with pain interference in the context of menstrual pain; indicating the importance of further studying the relationship between menstrual pain, psychological distress, and adolescent functioning.

TLR4 Immunoreactivity Differentiates Clinical Subtypes of Women with Interstitial Cystitis/Bladder Pain Syndrome

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating chronic disorder marked by

pain and urinary symptoms. with phenotypic heterogeneity that contributes to difficulty in diagnosis and treatment. Data from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network show that females with pelvic pain alone versus those with widespread pain are distinct subtypes (Schrepf et al., 2023). This study examines whether the ex vivo whole-blood stimulated inflammatory response to lipopolysaccharide (LPS), a potent toll-like receptor (TLR)-4 agonist, can reliably differentiate between these subtypes. Clinical symptoms (genitourinary pain, widespread pain, and urinary symptoms), healthcare utilization (HCU), and inflammatory response were assessed three times over an 18-month period. Participants were divided into two categories: those in the upper half of the distribution for inflammatory markers at all time points (n=38) and those in the lower half (n=34). Repeated-measures general linear models were used to assess difference in mean levels of symptoms from the three timepoints, with inflammatory group as the primary predictor of interest. For HCU events, a Poisson regression model was used to assess differences in HCU. All models controlled for participant age. Participants with consistently high level of inflammation showed greater genitourinary pain severity (p=.006), widespread pain (p=.006) and 2.5x more HCU events ($p<0.001$) than those with consistently low inflammation. There were no differences in urinary symptoms (p =. 415). These data suggest that consistently high peripheral immunoreactivity is associated with increased disease burden and widespread pain in female patients with IC/BPS.Funding: R01DK123164; K00HD11837.

A Pilot Yoga Intervention Improved Quality of Life Among Women with Dysmenorrhea Undergoing In Vitro Fertilization (IVF) Treatment

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Infertility affects millions of women, particularly those with endometriosis and dysmenorrhea, and is associated with worsened quality of life (QoL). Women increasingly undergo in vitro fertilization (IVF), which includes physical (hormonal treatment, invasive procedures) and emotional (unpredictability, disappointment) stressors. Yoga-based breathing exercises and physical movements represent a holistic approach for coping with discomfort and stress, although there is limited evidence within women undergoing IVF. The present study was a single-arm, non-randomized pilot trial of a yoga intervention designed for women undergoing IVF. All patients were instructed to practice 60-minutes of yoga weekly for 6 weeks, guided by a beginner-level yoga instructional video, which focused on breathing, self-awareness, and ways to modify poses to avoid pain. Before the intervention, patients completed sociodemographic, health history, and Fertility Quality of Life (FertiQoL; range:0-92) questionnaires. After the intervention, patients again completed the FertiQoL. Of the total sample (N=37), 26 patients (70%) completed both pre- and post-intervention questionnaires, and were included in the present analysis. Patients were an average age of 35.4 years (SD=3.7, range:29-45), 85% White, and 35% reported a history of dysmenorrhea (menstrual pain). On average, QoL significantly improved from pre-post intervention (M=55.8 vs. 61.3; $p<.05$). A follow-up analysis revealed that women with dysmenorrhea (pre: M=48.7 vs. post: M=60.0) experienced a significantly larger increase in QoL compared to women without dysmenorrhea (pre: M=59.6 vs. post: M=62.1) ($p<.05$). These findings suggest that a virtual yoga intervention improved QoL in

women undergoing IVF, and may be particularly beneficial for those with a history of dysmenorrhea.

Resilience among Adults with Chronic Urologic Pelvic Pain Syndrome: A Flexible Self-Regulation Perspective

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While flexibly responding to the burden of chronic pain requires psychological resilience (France et al., 2020), its core mechanisms have not been systematically isolated in high impact pain disorders like Urologic Chronic Pelvic Pain Syndrome (UCPPS). Applying a flexible self-regulation (FSR) model of resilience (Bonanno & Burton, 2013), we sought to characterize how flexibility deficits in the abilities to read, decode, and respond appropriately to contextual cues (context sensitivity; e.g., stressor controllability) and coping flexibility relative to known resilience (e.g., pain-specific resilience) and vulnerability (e.g., catastrophizing) factors, correspond with symptom severity and quality of life (QoL) impairment in patients with refractory UCPPS symptoms. Participants included 113 (Mage = 43.56, SD = 14.79, 81.4% female) formally diagnosed UCPPS (Interstitial Cystitis/Bladder Pain Syndrome or Chronic Prostatitis/Chronic Pelvic Pain Syndrome) patients with refractory pelvic pain. Baseline data, completed as part of an NIH clinical trial, included FSR components, Pain Resilience Scale, social support, Positive and Negative Affect Schedule, Coping Strategies Questionnaire - Catastrophizing, pelvic pain and urinary severity indices, and QoL (CDC Healthy days, PROMIS physical and mental health). Regression analyses, using a Bayesian variable selection method, were applied to examine how resilience and vulnerability factors predict symptom and QoL outcomes. As predicted, context sensitivity and coping flexibility corresponded with higher QoL. The pattern of results was stronger for components of FSR than for dispositional psychological factors including pain resilience, negative affectivity, and pain catastrophizing. Data demonstrates the importance of resilience rooted in a theory-informed, empirically grounded FSR model.

Descriptions Of Pain and Disability In Endometriosis Patients

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Endometriosis affects 10% of females who experience a broad spectrum of symptoms, severity and comorbid conditions that reduce quality of life. The aim of this study was to describe the characteristics of pain in patients with endometriosis and identify relationships between endometriosis health/pain and endometriosis symptoms and disability. Patients with endometriosis (n=16, mean age 27 years old, ±9.09, age range 13-45) completed surveys assessing pain, disability and comorbid conditions. On a 0-10 scale, menstrual pain intensity and unpleasantness were 6.9±2.1 and 6.1±2.6. Menstrual cramp intensity and unpleasantness were 6.7±2.5 and 5.9±3.0. The most common comorbid conditions were migraine (68.8%), back pain

(56.3%), and irritable bowel syndrome (50%). The cohort had high rates of clinically diagnosed anxiety and depression (87.5% and 62.5%). Functional Disability Index (FDI) scores showed moderate disability (17.1, range 0-60) and moderate global health status with the Endometriosis Health Profile Pain domain (54.12, range 0-100). Of the 13 sexually active participants who completed the Female Sexual Function Inventory Pain Domain, which examines pain during vaginal penetration, the average score was 3.2±1.3 (range 0-6) reflecting moderate pain. Endometriosis-related health status was significantly related to menstrual pain intensity ($r^2=0.352$, $p=0.025$), cramp intensity ($r^2=0.464$, $p=0.007$) and FDI scores ($r^2=0.484$, $p=0.004$). Endometriosis is a heterogeneous condition, and future research should further explore symptom presentations to better refine diagnostic criteria and treatments.

Sex Differences in Gut Serotonin-Mediated Signaling of Visceral Pain
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Visceral pain is a debilitating symptom of irritable bowel syndrome (IBS), a highly prevalent disorder that causes substantial morbidity and is 2-3 times more common in females. Serotonin (5-HT) signaling has a role in visceral pain, but treatments targeted to 5-HT are limited and fraught with adverse effects. Enterochromaffin (EC) cells in the gut epithelium release 5-HT, which can stimulate extrinsic primary afferent neuron (ExPAN) terminals to promote pain signaling. The serotonin reuptake transporter (SERT), present throughout epithelial cells, rapidly inactivates 5-HT. The present studies tested the hypotheses that 1) 5-HT released from EC cells and 2) SERT-mediated regulation of mucosal 5-HT availability modulate visceral nociception. Mice with a lack or excess of mucosal 5-HT underwent visceral nociceptive testing using the visceromotor response (VMR) assay. In loss-of-function experiments, TPH1 KO mice, wildtype mice treated with a peripheral TPH inhibitor drug, and TPH1-CreERT2-HM4Di displayed a sex-dependent decrease in visceral nociception. In gain-of-function experiments, mice harboring a gut epithelium-specific SERT KO (SERT-Floxed/Villin-Cre), as well as TPH1-CreERT2-HM3Dq mice, displayed a sex-dependent increase in visceral nociception. Surprisingly, in tamoxifen-inducible epithelial-specific SERT KO mice (SERT-Floxed/Villin-CreERT2), both males and females displayed decreases in visceral nociception. These data demonstrate that excess mucosal 5-HT can potentiate visceral nociception in males and lack of mucosal 5-HT can diminish visceral nociception in females. However, an inducible and prolonged increase in mucosal 5-HT has anti-nociceptive effects, possibly due to ExPAN 5-HT receptor desensitization. These studies indicate that 5-HT-targeted treatments for visceral pain may have different efficacy in males vs. females.

Finding a Gut-Pain Connection in Neurogenic Bowel Pain and Disorders
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Neurogenic bowel (NB) is a condition characterized by slow colonic transit, fecal incontinence,

and chronic abdominal pain that most often develops following damage to the central nervous system, as in traumatic spinal cord injury (SCI) or non-traumatic diseases such as Parkinson's disease. Since the molecular mechanisms of NB remain unknown, current treatments remain symptom-focused and are largely ineffective. Therefore, the primary goal of the present studies is to uncover the mechanisms underlying NB. Our lab has recently characterized a rodent model of moderate SCI resulting in NB phenotypes comparable in SCI patients. We found that peripheral calcitonin gene-related peptide (CGRP) is released into the colon after SCI. CGRP is a neurogenic inflammatory mediator released by primary sensory neurons that increases neuronal activity and induces pain. We have shown that intrarectal antagonism of CGRP significantly prevents NB phenotypes like colonic dysmotility, and neoplastic lymphoid hyperplasias of colon. Existing literature and studies from our lab link CGRP overexpression and release after SCI with the establishment of a proinflammatory environment within the colon and, potentially, induction of gut microbial dysbiosis. Interestingly, calcium imaging of nodose ganglion neurons in vitro revealed that colon-specific vagal afferents become hyperresponsive to fecal supernatants from SCI animals, suggesting a role for CGRP and the gut microbiome in sensitization of sensory afferents that carry nociceptive signals to the brain. Further studies on the impact of gut dysbiosis on pain development are currently underway to identify novel therapeutic targets to restore gut homeostasis and treat NB in SCI patients.

Managing Pelvic Pain Via Thermal Neuromodulation
Paolo Maccarini, Zack Lyon; Duke University

Pelvic pain (PP) affects millions, linked to conditions like Urinary Tract Infections, Endometriosis, and Interstitial Cystitis, severely impacting quality of life, work, and relationships. It contributes to significant opioid abuse, overdose deaths, and costs over $150 billion annually in the U.S. Current treatments, such as neural stimulation, may become ineffective long-term. H3Pelvic's Contrast Applied Therapy (CAT) system is non-invasive and uses a water-circulating membrane to modulate temperature delivery to the pelvic regions. It has shown promising results in relieving pain and improving daily activities for patients with refractory conditions like IC. We propose to enhance the system by integrating heat-pipe technology and real-time temperature tracking via passive microwave radiometry, creating the RICAT system. This will leverage smart radiometry and machine learning to optimize thermal modulation for pain relief. Phase I will integrate sensors, compare data with invasive methods, and test the system in pre-clinical settings. Success in Phase I will set the stage for Phase II clinical trials in refractory IC patients Funded by NIH Grant 1R43HD112219-01A1.

A Mixed-Method Examination Of Chronic Pain Stigma In Females With Chronic Pelvic Pain
Michaela Sawada, Jenna Wilson, Kylie Steinhilber, Jolin Yamin, Kristin Schreiber, Robert Edwards, Samantha Meints; Brigham and Women's Hospital

Chronic pelvic pain (CPP) is highly prevalent and associated with fatigue, anxiety, depression,

social isolation, and decreased health-related quality of life. Females with CPP report unsatisfactory interaction with healthcare providers, delays in diagnosis or misdiagnosis, and being labeled as "difficult" if they do not respond to healthcare treatment. As a result, women with CPP may experience increased rates of chronic pain stigma. This mixed-methods study aimed to characterize the experience of chronic pain stigma among females with CPP and examine the relationships between chronic pain stigma and health-related outcomes including pain. Seventy-nine females with CPP (Mage=36, SD=12.6; 56% White; 68% non-Hispanic) completed measures of physical function, anxiety, depression, fatigue, sleep, social roles, pain intensity and pain interference (Patient-Reported Outcomes Measurement Information System-29; PROMIS-29) and chronic pain stigma (Internalized Stigma of Chronic Pain; ISCP). A subset (N=20) of participants completed a 60-minute, semi-structured interview which investigated their experiences with chronic pain stigma. Results of Pearson correlations indicate moderate-to-strong positive relationships between chronic pain stigma and depression, anxiety, fatigue, sleep disturbance, pain intensity and pain interference (Rs=.284-.575, ps<.05). There were also moderate-to-strong negative relationships between chronic pain stigma and physical function, and social role engagement (Rs=-.297--.534; ps<.05). Results of preliminary thematic analysis indicate the following themes: stigmatizing beliefs, sources of stigma, outcomes due to stigma, and solutions for stigma. Results suggest females with CPP experience considerable chronic pain stigma which is associated with poor health outcomes. Interventions aimed at reducing chronic pain stigma, especially among females with CPP, are needed. University of Oklahoma Health Sciences Center, IBEST Award.

Results From A Pilot Study Evaluating Cortical Circuitry For Pain Modulation In Patients With Chronic Pain Using Opioids

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Understanding the effect of opioids on chronic pain processing is critical for effective pain management. This study utilizes a novel experimental protocol and quantitative EEG technology paired with semi-quantitative pain assessments to precisely evaluate pain modulation in opioid naïve and opioid-positive patients with chronic pain.

Participants with chronic pain(≥4/10 NRS), without severe concurrent medical conditions were recruited. Participants (n=15, 11 females) aged 60(±15.2 years old) taking opioids self-reported symptoms of pain intensity (5.1±1.7), pain interference(5.3±2.9), anxiety(53.9±8.6), depression levels (51.7±7.5), and sleep disturbance(58.2±7.3). A positive correlation was found between pain severity and pain interference(r=0.58). A weak positive correlation was found between pain severity and sleep disturbance(r= 0.2). No correlation was found between pain severity and depressive symptoms(r=0.08). When stratified by opioid usage, participants taking opioids had a stronger positive correlation between pain severity and depressive symptoms(r=0.3), while participants not on opioids showed slight negative correlation(r=-0.2). During the acute pain stimulation experiment, patients taking opioids had a negative correlation(r=-0.6) between lower pain threshold and pain severity. Targetting A-delta fibers for acute noxious stimulation at different intensities(low pain=2; high pain=5), participants received electrical stimulation on the index finger. EEG were placed on participants with 64 electrodes in an extended 10-20 system.

EEG analysis showed that the magnitude of pain evoked potentials reduced in participants taking opioids. Preliminary findings indicate that patients on opioids had lower pain magnitudes yet higher correlations with depressive symptoms. Continued evaluations combining EEG and self-report pain assessments may further define pain processing differences among those using opioids. (Funding: University of Oklahoma Health Sciences Center, IBEST Award).

Acute to Chronic Pain

Inhibition of PFKFB3-Driven Glycolysis Downstream of Inflammarafts in Spinal Microglia Alleviates Chemotherapy-Induced Neuropathic Pain

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Microglia and spinal cord neuroinflammation are pivotal in driving central sensitization and the progression of chronic pain following chemotherapy treatment. However, the phenotypic dynamics and molecular mechanisms underlying their contributions to pain remain poorly understood. To address this, we employed a mouse model of chemotherapy-induced peripheral neuropathy (CIPN) using two intraperitoneal injections of cisplatin (2.3 mg/kg/day). In this model, microglia undergo significant genetic and metabolic reprogramming, which contribute to the onset of chronic pain. Our study demonstrates that TLR4, a key immune receptor involved in inflammatory signaling, is localized within cholesterol-rich membrane lipid rafts, referred to as "inflammarafts." Notably, the deletion of cholesterol efflux transporters ABCA1 and ABCG1 in microglia of CIPN mice enhances TLR4 recruitment to lipid rafts, promoting a pro-inflammatory phenotype in the spinal cord. Furthermore, cholesterol-loaded microglia show elevated expression of PFKFB3, a glycolytic enzyme crucial for metabolic reprogramming. In CIPN mice, CD11b+/TMEM119+ spinal microglia exhibit increased chromatin accessibility at glycolysis-related genes, particularly Pfkfb3, with corresponding increases in both transcription and protein levels. Preliminary data reveal that inhibition of PFKFB3 (via intrathecal delivery of 3PO at 1.75 μg/5 μL or PFK-158 at 0.6 μg/5 μL) in inflammaraft-bearing microglia alleviates mechanical hypersensitivity and reduces inflammaraft formation in spinal microglia. These findings highlight the critical roles of lipid metabolism and glycolysis in microglial metabolic reprogramming during peripheral neuropathy. They also point to novel therapeutic targets, offering promising avenues for safer and more effective pain management strategies.

Longitudinal Associations Between Posttraumatic Stress Disorder Symptoms, Pain, and Physical Dysfunction Following Acute Orthopedic Injury

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There is a growing body of research linking PTSD symptoms to chronic pain, but our knowledge of these associations in the assessment and treatment of acute pain is limited. This is an important area of inquiry given that acute pain represents a key window in which to intervene to halt the development of chronic pain. Here we report on a secondary analysis examining associations between PTSD symptoms and pain outcomes over the course of treatment and 3-

month follow-up from a mind-body intervention for acute orthopedic injury. We used time-varying lagged mixed-effects models to examine longitudinal associations between PTSD symptoms anchored to acute orthopedic injury (PTSD Checklist) and outcomes: pain intensity (at rest and with activity) and physical dysfunction (Short Musculoskeletal Function Assessment). We also conducted exploratory analyses testing the interaction of time, treatment group, and PTSD diagnosis as moderators of changes from baseline to post-treatment and 3-month follow-up. We found that PTSD symptoms at baseline predicted pain intensity and physical dysfunction at post-test and that post-test PTSD symptoms predicted all outcomes at 3-month follow-up. We did not find moderating effects of PTSD diagnosis on treatment outcomes. Findings suggest that a mind-body intervention for acute orthopedic injury is effective regardless of PTSD status, but lingering PTSD symptoms after treatment are important predictors of longer-term pain. Results suggest potential use of stepped care treatment in which general mind-body skills are presented first before specialized PTSD treatment is utilized for non-responders.

Reducing Opiate Use for Chronic Pain: Patient and Provider Experiences of a Deprescribing Intervention

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Between the years 1999 and 2018 over 450,000 people died of opioid overdose. Clinical practice guidelines recommend discontinuing opioids whenever possible for most patient groups. There is extensive literature describing the negative effects of opioids since abrupt, nonvoluntary discontinuation has been associated with patient harm and is not recommended. In 2017, Cabarrus Family Medicine successfully eliminated virtually all opioid prescribing at a clinic. Of 376 patients on chronic opioids, 76% tapered off and remained at the clinic one year after the intervention. The majority of those who did not taper off transitioned their prescription to pain management and remained at the clinic. The intervention was successful in reducing opioid prescriptions by practice providers, but patients' and providers' perceptions of the practice change were not evaluated. Surveys and key informant interviews were conducted from 2022 through 2024. Of the original 376 patients, 222 (60%) are still at the clinic and they were contacted. Five providers had an overall positive perception of the intervention as they were no longer responsible for prescribing opioids. Of the 46 patients who responded to the surveys, over 50% experienced a negative quality of life impact and higher pain levels since the practice change. More than 50% indicated their overall health was much worse, but less than 3% stated the practice change negatively impacted the relationship with their provider, and less than 5% experienced withdrawal symptoms. Patients frequently stated that an authority above their provider mandated the change and their provider supported them through it.

Characteristics of Emergency Department Patients with Pain: A Novel Remote Research Study in 10 Pennsylvania Emergency Departments

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Despite long standing recognition of individual disparities in acute pain presentation and management, individuals affected by these disparities are often underrepresented in research. We are enrolling a large cohort of patients from emergency departments (ED) across Pennsylvania to characterize social determinants of health in patients seeking ED treatment. A total of 401 patients (M age = 36.5; Range: 18-88) with a pain score of at least 4/10 seeking ED treatment in one of 10 participating hospitals voluntarily scanned a QR code for study enrollment (enrollment is ongoing). To date, most participants are female (70%), White (63%) or Black (24%), with at least high school (35%) or some college education (>60%); 25% report unemployment. About 38% reported income that falls beneath the 2024 federal poverty line. Reasons for seeking ED treatment ranged from ongoing health problems (41%), new health problems (34%) or acute accident or injury (25%). On average, pain score was (M = 7.36; SD = 1.89); the most prevalent location for painful complaints were lower back and abdomen (35%), followed by head and neck (>20%). In the past year, ED participants reported various barriers to getting healthcare: couldn't get an appointment as soon as needed (25%), transportation problems (19%), worry about cost of medication (19%), and worry insurance won't cover cost (18%). In general, pain score was higher for nonwhite participants and those with income below the poverty line. This data may serve to identify opportunities to improve to optimize pain-related and general health outcomes of ED patients.

Functional Characterization of MRGPRD Receptors in Human Induced Pluripotent Stem Cell- Derived Sensory Neurons In Microfluidic Culture Devices

Abdelhak Belmadani, Dongjun Ren, Nirupa D Jayaraj, Paola Pacifico, Vince Truong, Patrick Walsh, Daniela M Menichella, Richard J Miller, Anne-Marie Malfait; Northwestern University

The human MRGPRD protein is a member of the Mas-related G protein-coupled receptors (MRGPRs) that is involved in the sensing of pain, itch, and other inflammatory stimuli. The most potent small-molecule agonist of MRGPRD reported so far is b-alanine, with an affinity in the micromole range. In ex vivo studies, activation of MRGPRD enhances the excitability of primate nociceptive neurons. Thus, MRGPRD medications have potential utility for the treatments of a number of sensory disorders, including pain. In this study we looked to functionally characterize MRGPRD receptors expressed in human induced pluripotent stem cells (hiPSCs)(RealDRG) in microfluidic coculture devices that can be used to test new designed high affinity MRGPRD agonists. First, we found that RealDRG cells can be differentiated into sensory neurons (RealDRG) of different maturation potentials as early as 2 weeks in monoculture using small molecules and growth factors in monocultures. Using calcium imaging recording, we found that the neurons respond to b-alanine in a dose dependent manner as early as two weeks. Using RNAScope, we further found that these cells exhibit strong inward/outward currents with high expression of Nav1.7 and very low levels of TRPV1 expression. However, these cells did not express Nav1.8, or respond to capsaicin, indicating that these cells are transcriptionally different compared to murine DRG or postmortem human DRG neurons, potentially limiting their usefulness as a full fledge nociceptor cell model. In order to address this limitation, and promote their maturation potentials, we used this transcription factor-based differentiation methods in compartmentalized microfluidic coculture system, cocultured RealDRGs with human synovial

fibroblasts (hsFBs) to model crosstalk in osteoarthritis knee joints and looked to functionally characterize MRGPRD receptors expression in RealDRGs. Using hsFBs in coculture with RealDRGs for a maturation period between 2 to 6 weeks, we found that ReaDRG were able to grow neurites that formed tight connections with sFBs. We further found that the majority of the cells responded to b-alanine with a significant difference in number and intensity in RealDRG neurons compared to monocultures without hsFBs. There was also an increase in the number of capsaicin-responsive neurons. RNAScope experiments are ongoing to determine the potential impact of hsFBS on MRGPRD expression and trafficking. Together, these findings demonstrate that hsFBs are able to induce greater functional maturation of RealDRGs, potentially due to MRGPRD signaling pathways that maybe activated through paracrine signaling, and direct contact. This could be harnessed to accelerate the search and the discovery of high-affinity MRGPRD agonists for this important and understudied receptor. NIH P30AR079206.

Activation Of The Nuclear Factor Erythroid 2-Related Factor 2 Pathway Over Time In Chronic Neuropathic Pain Model

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Oxidative stress has been a widely known factor to result in the development of neuropathic pain. Luckily, our system has a process that combats the emergence and buildup of oxidative stress via the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. The Nrf2 pathway has been widely studied throughout various pain models, but there is still limited knowledge about the causal relationship between Nrf2 activation and neuropathic pain reversal. We studied the role of Nrf2 in chronic pain using a chronic constriction injury (CCI) pain model. The requirement of Nrf2 for prevention of neuropathic pain was assessed after mild CCI in Nrf2 knockout mice using various allodynia models. Pharmacological inhibition of Nrf2 was also tested. We found that genetic deletion and pharmacological inhibition of Nrf2 exacerbated mechanical, dynamic, and cold allodynia after mild CCI. The length of Nrf2 activation was quantified by western blot in the ipsilateral dorsal root ganglia (DRG) after CCI. Nrf2 activation was found to steadily increase throughout days 1 and 3 following nerve injury and dropping after day 7 and kept decreasing after day 14 and 21, reaching near baseline. qPCR revealed that several genes related to the Nrf2 pathway were altered after CCI surgery in the central and peripheral nervous system. Oxidative stress was also measured following nerve injury and reached significant increase on day 21 for nitrotyrosine and 4-hydroxynonenal. These findings demonstrate Nrf2 as an essential protein in preventing the development of pain behaviors and validates Nrf2 as a therapeutic target in neuropathic pain.

Neuroinflammation in the Primary Somatosensory Area is associated with Pain Widespreadness in Individuals with Chronic Low Back Pain

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Our laboratory has shown that patients with chronic pain conditions, including chronic low back pain (cLBP), demonstrate elevated 18 kDa translocator protein (TSPO) positron emission tomography (PET) signal, a putative marker of neuroinflammation. Here, we explored the association between neuroinflammation in the primary somatosensory cortex, which contains the somatosensory representation of the entire body, and clinical presentation of cLBP. Specifically, we hypothesized that increased neuroinflammation in the post-central gyrus (PCG) would be correlated with increased pain widespreadness in the lower back. Using integrated 3T positron emission tomography/magnetic resonance imaging and the TSPO PET radioligand [11C]PBR28, we scanned 40 patients. Using digital pain drawings that dynamically captured patients' cLBP symptoms (Neubert et al., et al 2018), we computed the widespreadness of each patient's clinical pain symptoms within the back area. In region-of-interest analyses, we found that the average Standardized Uptake Value Ratio (SUVR) extracted within the PCG label from the Harvard Oxford Cortical Atlas (threshold=30) significantly predicted increased lower back pain widespreadness ($r=.33$; $p<.03$). Additionally, voxelwise analyses using the same label as the pre-threshold mask (FSL FEAT OLS, voxel-corrected using a voxel P threshold of $p<.05$) revealed a significant cluster in the PCG area, lateralized to the left hemisphere (peak z-stat: $x=64$; $y=52$; $z=58$). Overall, these results establish an association between neuroinflammation and a clinical symptom (i.e., pain widespreadness) in cLBP, highlighting the clinical significance of TSPO signal elevation observed in chronic pain.

Outcomes Evaluated By Transitional Pain Services: A Systematic Review

Alexandra Sideris, Angelina Colamarino, Charles Lok, William Chan, Ha Young Cho, Bridget Jivanelli, Faye Rim, Joseph Manne, Lisa Doan; Hospital for Special Surgery

Transitional Pain Services offer multidisciplinary programs that incorporate preventative strategies and offer personalized, multimodal treatments to ensure adequate postoperative pain control during hospitalization, and continuity of care in surgical patients who are at increased risk for experiencing opioid-related adverse events and developing chronic post-surgical pain. To better understand how formal Transitional Pain Services evaluate the effectiveness of their programs, we conducted a systematic review of studies that quantified the impact of their interventions in non-cancer surgical patients, and described components of the programs, patient populations, and outcomes assessed. A total of 1,373 abstracts from papers published through 2023 were screened, and 20 manuscripts ultimately reviewed for data extraction. Differences exist in the care delivery models and targeted outcomes. Most published studies (18/20) were retrospective analyses of existing data between 2014 and 2022 from hospitals located in urban settings in five different countries, primarily included patients who underwent elective surgeries including orthopedic, cardiothoracic, obstetric and gynecological procedures, included opioid-naïve and opioid-experienced patients, and compared patients in Transitional Pain Service programs against either historical controls prior to program implementation or matched patients who did not utilize the services. Outcomes assessed included opioids at discharge in morphine milligram equivalents (n=6), and post-discharge opioid use at 60 days (n=2), 3 (n=6), 6 (n=4), and 12 (n=2) months. Patient- reported pain outcomes were assessed in 5 studies, and included either pain intensity measures, pain interference, or pain catastrophizing. Less frequently

reported outcomes were postoperative complications, quality of recovery and 30-day readmissions. Funding: CV Starr Foundation.

Assessing Pain Distributions in Spinal Conditions using the CHOIR Body Map
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Spinal conditions are a leading cause of pain. The pathophysiology of spinal conditions is complex leading to varying distributions of pain across patients. We conducted a cross-sectional analysis of a large cohort of patients from a multidisciplinary tertiary care pain clinic to understand the pain patterns associated with different spinal conditions. Using diagnosis codes, we identified patients with cervical spine conditions without radiculopathy or myelopathy (n=2,255), with cervical radiculopathy (n=321), and with cervical myelopathy (n=267) as well as patients with lumbar spine conditions without radiculopathy or spinal stenosis (n=4,139), with lumbar radiculopathy (n=879), and with lumbar spinal stenosis (n=824). We examined pain distributions using the Collaborative Health Outcomes Information Registry (CHOIR) body map. In cervical spine conditions without radiculopathy or myelopathy, pain was most frequently reported in the posterior neck and head. In cervical radiculopathy, pain extended most frequently into the upper back and shoulders. In cervical myelopathy, upper limb pain was less frequently reported in comparison to cervical radiculopathy. In lumbar spine conditions without radiculopathy or spinal stenosis, pain was most frequently reported in the low back. In lumbar radiculopathy, pain extended into the lower limb and most frequently into the buttocks. In lumbar spinal stenosis, lower limb pain was less frequently reported in comparison to lumbar radiculopathy. We identified different patterns of pain distributions between spinal conditions with and without neurological injury. Future research will incorporate additional pain measures, including severity and duration, and investigate changes in pain distributions before and after pain management procedures. Funding: R01NS128478.

Psychosocial Predictors of Changes in Pain Sensitization During the Transition from Acute to Persistent Low Back Pain
Katherine Gnall, Mariel Emrich, Tania Huedo-Medina, Crystal Park, Angela Starkweather; University of Connecticut

The transition from acute to persistent low back pain (LBP) is marked by central and peripheral somatosensory changes, making it a critical period for intervention targets. Whether cognitive (e.g., catastrophizing) or emotional (e.g., mood disturbance) factors during the acute period predict changes in sensitization over time remains unexplored and is the aim of the present secondary analysis. Adults (N=146; Mage = 31.9, 50% female, 54.8% Black/African American) with acute low back pain (greater than 24 hours and less than 4 weeks, preceded by greater than 1 pain-free month) completed assessments at baseline (T1) and 3-month follow-up (T2). Quantitative sensory testing (QST) measures (mechanical pain sensitivity (MPS); cold pain threshold (CPT); and pressure pain threshold (PPT)) at the pain site and a control site were used

to measure peripheral and central sensitization. Participants also completed self-report surveys (e.g., Coping Strategies Questionnaire-Revised; Profile of Mood States). Separate generalized linear models (GLMs) were used to examine the predictive role of T1 cognitive/emotional factors on T2 QST, controlling for T1 QST, age, sex, and household income. Catastrophizing predicted change in MPS (B=.021, p=.027), and PPT (B=-.01, p=.045) at the control site, controlling for covariates. Mood disturbance predicted change in MPS at the pain site (B=.004, p=.011), controlling for covariates. Catastrophizing and mood disturbance did not significantly predict any other QST measures. Findings suggest both catastrophizing and mood disturbance during the acute injury period predict aspects of increased peripheral and central sensitization during the transition to persistent LBP, offering important insight into treatment targets following acute back injuries.

Dermal Fibroblasts Modulation by Post-Herpetic Neuralgia
Emily Debner, Andreas Chavez, Frank Rice, Michael Burton; University of Texas at Dallas

Peripheral Herpetic Neuralgia (PHN) is a painful neuropathic condition caused by nerve damage during viral reactivation and characterized by persistent pain after visible signs of infection have resolved. Sensory neurons have been the primary focus of PHN research, however non-neuronal cells in the skin can participate and drive various pain states. Our lab has shown dermal fibroblasts are a central player in pain initiation and persistence. During PHN, fibroblasts can be directly activated by the virus and also by pro-inflammatory molecules present during infection. In other cell types, such as macrophages and microglia, morphological changes and calcium signaling indicate functional shifts and activation states. We hypothesized dermal fibroblast morphology during painful PHN is indicative of function and pain. To date, no one has investigated the role of human fibroblasts during PHN. Initially, we assessed fibroblast morphology in PHN patient skin collected from painful and non-painful dermatomes. Fibroblasts from painful PHN dermatomes have significantly greater volume compared to non-painful dermatomes, regardless of sex, suggesting fibroblasts may be in an activated state and contributing to pain in PHN. To begin to understand how fibroblast may contribute to pain caused by viral infections, we assessed fibroblast calcium responses to the viral mimetic Polyinosinic:polycytidylic acid (Poly I:C). Pretreatment with 1μg/mL Poly I:C for 5-mins or 24-hours significantly increased fibroblasts response to ATP, a major signaling molecule in the skin, compared to control. Together with the data from painful PHN skin, this suggests that fibroblasts respond viral infections, potentially contributing to pain in PHN.

Targeting NaV1.7: A Structural Framework for Next-Generation Pain Therapeutics
Samantha Perez-Miller, Rajesh Khanna; University of Florida College of Medicine

The voltage-gated sodium channel NaV1.7, localized peripherally, plays a crucial role in initiating action potentials. Gain-of-function mutations in the human NaV1.7 gene lead to sensory neuron hyperexcitability and severe pain, while loss-of-function mutations cause congenital insensitivity to pain. Despite being a validated and highly sought-after drug target for treating neuropathic pain conditions, NaV1.7-targeting drugs have yet to reach the clinic. The

recent decade has witnessed a paradigm shift in our understanding of NaV1.7 interactions with known effectors, providing a near-atomic level view of these interactions. Pioneering structural insights were unveiled by the Payandeh lab, who ingeniously fused a bacterial channel with the fourth voltage sensing domain of NaV1.7. This chimera, along with another constructed by the Yan lab using the second voltage sensing domain, unveiled interactions with peptide toxins, another potential source of NaV1.7 targeting drugs. Recent advancements in cryo-electron microscopy techniques have enabled both the Yan and Jiang research groups to obtain the structures of human NaV1.7 with over a dozen different effectors bound. We will curate these structures into a comprehensive visual library, meticulously comparing binding sites and structural alterations to identify strategies for enhancing the selectivity and potency of NaV1.7-targeting pharmacological agents.

Tonic Inhibition of Colorectal Afferent Mechanotransduction by Group III Metabotropic Glutamate Receptor mGluR7

Jia Liu, Bin Feng; University of Connecticut

Chronic visceral pain, which characterizes the prevalent disorders of gut-brain interactions (DGBI), is typically triggered by mechanical distension of hollow visceral organs like the distal colon and rectum (colorectum). All extrinsic afferents innervating the colorectum are glutamatergic excitatory neurons expressing a full spectrum of ionotropic and metabotropic glutamate receptors (iGluR and mGluR) at their sensory endings in all layers of the intestinal wall except the serosa. In addition, colorectal glutamate signaling is strongly indicated by the presence of glutamatergic myenteric neurons that project to virtually every myenteric ganglion. In this study, we focused on the role of mGluR7, a Gi-coupled inhibitory receptor with the highest expression level among all glutamate receptors in colonic afferent neurons. By conducting extracellular single-fiber recordings in an ex vivo colorectum-nerve preparation, we showed that intracolonic MMPIP, a selective mGluR7 antagonist, not only triggered spontaneous spiking of colorectal afferents but also enhanced the neural encoding of colorectal stretch and distension. In addition, blocking the L-type calcium channels with nifedipine abolished MMPIP's effect in triggering spontaneous spiking of colorectal afferents but did not completely negate its effect in sensitizing the afferents to colorectal stretch. On isolated longitudinal colorectal strips, MMPIP increased the frequency and magnitude of spontaneous muscle contractions. These compelling findings strongly indicate the tonic inhibition of colorectal afferents by inhibitory glutamatergic signaling via mGluR7, partly through the inhibition of longitudinal smooth muscle tone. Targeting mGluR7 could offer a promising therapeutic approach for managing visceral pain in DGBI. Funding: NIDDK R01 DK120824 Grant awarded to BF.

Summoning CRMP5: A New Guardian Against Neuropathic Pain

Clémence Gieré, Liberty François-Moutal, Laurent Martin, Aubin Moutal; Saint Louis University

CRMP5 is a protein involved in axonal growth selectively expressed in adult sensory neurons in the dorsal root ganglia after maturation of the nervous system. Auto-antibodies targeting CRMP5

in peripheral cancers induce neuropathic pain in approximately 80% of patients, but the underlying mechanisms are not well understood. We investigated the role of CRMP5 in pain behaviors in naïve rats and in a model of chronic neuropathic pain. Through genetic manipulation using siRNAs, CRISPR/Cas9 and lentivirus, we assessed the impact of a transient or complete knockdown of CRMP5 in the spinal cord of naïve rats on mechanical and thermal nociceptive thresholds. Conversely, in a model of Spared Nerve Injury where CRMP5 is severely downregulated, we evaluated if its re-expression could alleviate neuropathic pain symptoms. Disruption of CRMP5 expression in the spinal cord of naïve rats decreased mechanical thresholds suggesting its involvement in the development of mechanical allodynia. In rats with chronic neuropathic pain, promoting CRMP5 expression rescued mechanical and thermal thresholds. Together, these result place CRMP5 at the forefront of nociceptive sensitivity modulation in various mechanical, heat and cold modalities. These results show that CRMP5 expression in primary afferent fibers and spinal cord neurons plays a key role in maintaining normal pain thresholds and that restoring CRMP5 expression alleviates neuropathic pain symptoms. Therefore, CRMP5 emerges as a promising non-opioid therapeutic target for pain management.

Rates Of Injury Across The Disease Course Of A Chronic Overlapping Pain Condition
Sonia Sharma, Gary Slade, Hanna Grol-Prokopczyk, D. Brad Rindal, Paul Durham, Werner Ceusters, Barry Smith, Richard Ohrbach; University at Buffalo

Tissue damage is central to the definition of pain, and injury is a plausible locus for nociceptive, inflammatory, or both types of pain. We previously reported that rates of painful temporomandibular disorder (TMD) incidence were significantly higher among individuals who experienced jaw injuries (5.37/100-person-years; 95%CL=4.19-6.87) than those who did not (3.44; 2.8-4.14). Here, we used data from a 24-month prospective study, concurrent with the below-listed TMD histories, assessing injury at 3-month intervals to estimate rates (per-person-months (95%CL)) of 1) extrinsic event exposure, such as tooth extraction, oral intubation, or motor vehicle accidents; 2) extrinsic jaw injury, attributed to extrinsic events; and 3) intrinsic jaw injury, attributed to yawning and sustained mouth opening. Rates were calculated for four mutually-exclusive groups of adults classified according to TMD history of disease chronicity, each compared to a non-TMD reference group. Rates of extrinsic events were not significantly higher in any TMD group versus those who never had TMD. Rates of extrinsic and intrinsic injury were significantly higher in the following groups compared to those who never had TMD [extrinsic=0.48 (0.25-0.83); intrinsic=0.55 (0.3-0.93)]: 1) Individuals with only prior painful TMD [intrinsic=2.39 (1.27-4.09)], 2) individuals whose TMD pain had not resolved 30days after first-onset [extrinsic=1.95 (1.09-3.21); intrinsic=4.02 (2.73-5.71)], and 3) individuals with chronic painful TMD [extrinsic=1.41 (0.88-2.13)]; intrinsic=5.89 (4.75-7.22)]. In summary, intrinsic injury is reported at increasing rates as TMD history shifts from prior to persistent, which may reflect both greater susceptibility to injury due to disease progression and injury's contribution to disease progression.

Preliminary Effects of Diet on Factors Related to Chronic Knee Osteoarthritis
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AbstractDiets have been shown to have significant impacts on chronic pain outcomes, like knee osteoarthritis (KOA). We have previously shown that a low-carbohydrate diet (LCD) can reduce symptoms related to chronic KOA. However, our previous works did not include diverse populations. We sought to compare the benefit of an LCD with the USDA diet on measures of self-reported pain for adults living with KOA in a larger diverse sample. Forty adults with KOA were recruited and assigned to a 6-week LCD or a 6-week USDA-diet intervention. Measures of weight, bone mineral density, blood metabolic features, pain severity and interference, disability, physical functioning, gait, and overall chronic pain were taken at baseline and at 6-weeks of the assigned intervention. In addition, measures of diet satisfaction and effectiveness were taken 6-weeks of the assigned diet.Overall, all participants showed significant differences in weight, bone mineral density, self-reported measures of daily pain, pain severity and interference, pain disability, gait speed, and blood glucose levels. However, there were no significant differences for these measures based on diet assignment. Yet, there was a significant difference in perceived diet satisfaction that favored the LCD. Both diets provided a range of benefits related to self-reported symptoms related to pain for adults with KOA. The utilization of either an LCD or USDA-diet could both be applied as a modifiable and non-pharmacological additive treatment mechanism for chronic KOA. Funding: This project is supported by grant R01-NR020523 (RES, BRG) from the National Institute of Nursing Research.

Neutrophil Depletion Results in Prolonged Mechanical Hypersensitivity
Aaryn Edwards, Geoffroy Laumet; Michigan State University

Neutrophil Depletion Results in Prolonged Mechanical HypersensitivityAaryn Edwards, Geoffroy Laumet; Michigan State UniversityIt is well established that the immune system contributes to the development of chronic pain, but the intricacies of how immune cells, specifically neutrophils, are important for the resolution of pain remains under investigation. The aim of this study is to take a closer look at neutrophils' role in inflammatory pain resolution and gain a better understanding of how they influence other immune cells. By employing an established inflammatory pain mouse model, intraplantar injection of complete Freund’s adjuvant (CFA), we investigated the impact of depleting neutrophils on mechanical sensitivity as well as the effect on the immune response. To deplete neutrophils systemically, anti-Ly6G was injected intraperitoneally every three days following the onset of inflammation. Mechanical hypersensitivity was assessed using the von Frey method over the course of two weeks. The overall response of immune cells was observed and neutrophil depletion was confirmed using spectral flow cytometry. Depleting neutrophils in mice led to prolonged and increased mechanical hypersensitivity in the inflamed skin. It was also seen that neutrophil depletion modified the systemic immune cell response, showing an increase in lymphocytes and a slight decrease in macrophages. We showed that the reduction of neutrophils results in prolonged

inflammatory pain and a chronic inflammatory immune response. This data suggest that promoting neutrophil activity might be a new therapeutic strategy to alleviate chronic inflammatory pain. NIH (R01AI177305-01) NHERF1.

Machine Learning-Driven Predictive Modeling for Opioid Use Disorder in Chronic Pain Patients on Long-Term Opioid Use

Yoonjae Lee, Christal N. Davis, Peggy A. Compton, Rosemary C. Polomano, Martin D. Cheatle; University of Pennsylvania

The development of opioid use disorder (OUD) among patients with chronic non-cancer pain (CNCP) receiving long-term (≥6 months) opioid therapy for pain is a significant concern. Machine learning (ML) algorithms can help identify these patients at risk for OUD. Although several ML algorithms are constructed to predict OUD among general populations, there is a need for a model tailored to CNCP patients, given their unique risk factors related to prolonged exposure to prescription opioids. We sought to develop and validate a predictive model among 1,331 patients without OUD prior to receiving long-term opioid therapy for the treatment of CNCP. Of these patients, 430 later developed OUD, and 901 did not. The predictive ML model integrated biopsychosocial factors, including sociodemographic factors, pain characteristics (pain severity, interference), nicotine dependence, psychological symptoms (depression, anxiety, pain catastrophizing, mental defeat, suicidality), and social support. We evaluated the predictive performance of three ML algorithms: (1) logistic regression, (2) random forest, and (3) gradient boosting. Model performance for each was assessed using 10 folds cross-validation. Of the three models, the random forest algorithm achieved the best performance with an area under the receiver operating characteristic curve of 0.89. A feature importance analysis identified nicotine dependence, age, and pain catastrophizing as the top three significant features used for predicting OUD. This model not only offers a strong predictive framework, but also lays the groundwork for more advanced ML models that make use of a broader range of variables, ultimately improving early identification and intervention strategies for at-risk patients.

Extracellular Vesicles Mediate Keratinocyte-to-Neuron Bidirectional Communication in Painful Diabetic Neuropathy

James Coy-Dibley, Nirupa Jayaraj, Dongjun Ren, Paola Pacifico, Abdelhak Belmadani, Yi-Zhi Wang, Kamil Gebis, Jeffrey Savas, Amy Paller, Richard Miller, Daniela Menichella; Northwestern University

Painful diabetic neuropathy (PDN) is a debilitating complication of diabetes with patients suffering from a painful, burning sensation in their extremities. Current available treatments have limited effect in masking the pain without remediating the underlying mechanisms of the disease. The cellular hallmarks of PDN are cutaneous nerve-fiber degeneration and the hyperexcitability of the DRG neurons. Epidermal keratinocytes are closely juxtaposed to cutaneous nerve terminals in the skin, presumably enabling bidirectional communication between keratinocytes and cutaneous nerves. Extracellular vesicles are secreted nanovesicles that can produce

substantial transcriptional and translational changes. The role of keratinocyte-derived extracellular vesicles (KDEVs) in keratinocyte-to-neuron communication in PDN is unknown. Using primary adult mouse keratinocyte cultures, we characterized KDEVs for the first time in the established high-fat diet (HFD) induced mouse model of PDN. We performed a robust molecular characterization with proteomics and RNAsequencing in mice and found significantly altered cargos between HFD and regular diet control KDEVs. We also used two new in vivo conditional EV reporter mouse lines to show the bidirectional communication between keratinocytes and DRG neurons via the axonal transport of their respective extracellular vesicles: keratinocyte-originating nanovesicles are retrogradely trafficked into the DRG neuron cell body while DRG neuron-originating nanovesicles are anterogradely trafficked to the skin. These data suggest a potentially new communication axis for the regulation of DRG transcriptome and proteome regulation originating from the skin and vice versa. Our results could be translated into new topical interventions and therapies for both small-fiber degeneration and neuropathic pain in diabetes.

The Mind-Body Connection: Perceived Stress, Pain, and Structural Correlations Among a Pediatric Chronic Pain Population

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Introduction: The experience of stress, ranging from daily perceived stress to more severe adversity, has been posited as a primary catalyst for nervous system sensitivity and chronic pain vulnerability via functional and volumetric alterations, but minimal research has investigated these links. The current study aims to examine the association between perceived stress, adversity, pain, and hippocampal structure in youth with chronic widespread pain – a common pain condition.
Methods: This study is ongoing but to-date, 15 youth with CWP have been recruited and completed baseline self-report questionnaires and fMRI (Mean age = 15.5; 83% female). For each subject, structural MRI data were processed via FreeSurfer v.7.4 software package. Following, all data analyses were run through SPSS V. 29.
Results: Correlation analyses found that perceived stress was significantly and positively associated with adversity exposure ($r = 0.65$; $p = .009$), pain catastrophizing ($r = 0.48$; $p = .046$), anxiety symptoms ($r = 0.68$; $p = .003$), depressive symptoms ($r = 0.66$, $p = .003$), and functional disability ($r = 0.73$; $p = <.001$). Moreover, via one-way ANOVAs, we found significant associations between the left hippocampal volume (HV) and depressive symptoms ($p=0.028$) and between patient's highest pain intensity and both left ($p=0.03$) and right ($p=0.045$) HV.
Discussion: As anticipated, we found associations between brain structure, pain intensity, and psychosocial disability in youth with CWP. This supports the mind-body connection in pain vulnerability and focus on stress and adversity alleviation for long-term morbidity prevention. Future research should continue to examine these associations. Funding: NIH K23.

Associations Of Source And Continuity Of Private Health Insurance With Prevalence Of

Chronic Pain Among U.S. Adults

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Coverage by private insurance is associated with lower chronic pain prevalence (Semaan, 2024), but the significance of different types of private coverage for the epidemiology of chronic pain is poorly understood. We compared the prevalence of chronic pain among privately insured adults based on coverage source, coverage continuity, and relation to the policyholder using the 2019-2021 and 2023 rounds of the National Health Interview Survey. The primary outcome was pain prevalence. Among respondents with chronic pain, secondary outcomes included experiences of severe pain, high-impact pain, and opioid use. Based on the entire analytic sample, we estimated that 16% of adults ages 18-64 with private coverage had chronic pain, 10% had privately purchased insurance (as opposed to employer-sponsored), 4% experienced coverage gaps within the past year, and 33% were covered by a relative's policy (vs. own policy). On multivariable analysis, compared to adults with ESI, those with privately purchased insurance had lower odds of reporting chronic pain (OR: 0.86; 95%CI: 0.78, 0.95; p=0.004). Compared to adults with continuous private insurance coverage, those who experienced coverage gaps in the past year had higher odds of chronic pain (OR: 1.28; 95%CI: 1.11, 1.47; p<0.001). There was no difference in chronic pain prevalence based on relation to the policyholder and no differences in any secondary outcomes based on the study exposures. These results suggest that protecting the continuity of private coverage may help improve pain management and control the population prevalence of chronic pain.

Lysophosphatidylserine/GPR34 Signaling in Neuropathic Pain

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Neuropathic pain continues to be a huge unmet medical need; a better understanding underpinning its molecular signatures is poised to discover novel therapeutics. Our unbiased transcriptomic approach in a rodent model of traumatic nerve injury-induced neuropathic pain revealed that the Gi/o protein-coupled receptor (GPCR) GPR34 increases in the dorsal horn of the spinal cord ipsilateral to nerve injury. GPR34 is present in both humans and rodents and is highly expressed in microglia. Its primary endogenous ligand is lysophosphatidylserine (LysoPS). Little is known about the roles of LysoPS/GPR34 in pain. Chemical probes for GPR34, especially antagonists, are limited and have poor physicochemical properties limiting clinical utility. Using the cryoEM structure of GPR34, we designed and synthesized various analogs with GPR34 antagonistic activity and improved properties. Systemic and intrathecal (i.th.) administration of these antagonists in rodents reversed behavioral hypersensitivities in two models of neuropathic pain identifying the spinal cord as a potential site of GPR34 antagonist activity. LysoPS (i.th.) in rodents recapitulated behavioral phenotypes seen in the nerve-injury models and evoked dose- and time-dependent pertussis toxin-sensitive (Gαi/o-linked) behavioral hypersensitivities that were blocked by GPR34 antagonists. Our data lead us to hypothesize that microglial GPR34 in the spinal cord is a non-opioid based target for therapeutic intervention with GPR34 antagonists and the analgesic actions of GPR34 antagonists result from attenuating mitogen-activated protein kinase signaling in microglia. Funded by NIH grant R61NS138976.

Basic Science- Preclinical

Efficacy Of Tomivosertib (MNK1/2 Inhibitor) In Mitigating Pain In A RDEB Mouse Model
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Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a rare genetic disease caused by biallelic variants in COL7A1 and characterized by blistering, inflammation, and scarring. RDEB patients experience neuropathic pain, exacerbated during dressing changes and treated with morphine and gabapentin. The MAP interacting protein kinase (MNK) signaling pathway plays a role in neuropathic pain through modulating neuronal sensitivity. We hypothesized that the MNK pathway is activated in and contributes to chronic pain in RDEB. We employed mice with biallelic Col7a1 variants as a model for RDEB, exhibiting similar blistering and “mitten” acral scarring deformities, as well as pain behaviors seen in RDEB patients. mRNA expression of MNK pathway components (MNK, elF4E, Bdnf, Par2, Il6ra) was upregulated in the dorsal root ganglia (DRGs) of RDEB mice by 2-4-fold compared to wildtype littermates (all $p<0.05$). Similarly, phosphorylated eIF4E, a downstream target of MNK1/2, was increased in RDEB DRGs, suggesting hyperactivation of MNK signaling in RDEB nerves. Daily intraperitoneal injections of the MNK inhibitor, tomivosertib, reduced expression of Bdnf, MNK, Spry2, Eif43 compared to vehicle in RDEB mice. However, expression of Tac1, a downstream effector of IL4R/IL13RA1 signaling, which augments itch, was unchanged. Mouse pain behaviors (excessive grooming, paw nibbling, and facial grimacing) were observed, and duration of pain behavior was significantly decreased (50%; $p<0.05$) in RDEB mice treated with MNK inhibitor versus the vehicle control. Our preliminary findings identify a basis for pain in RDEB. These results suggest that targeting the MNK pathway with tomivosertib is a promising new therapeutic direction in RDEB management.

Functional Interrogation Of 5HT3R+ Sensory Neurons In Naïve And Arthritic Mice
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The aim of the current study was to map the distribution, phenotype and function of 5HT3AR positive sensory neurons in the normal and inflamed mouse knee joint. We delivered Flp dependent excitatory optogenetic (AAV-CAG-fDIO-ChrimsonR-tdTomato) and inhibitory chemogenetic (AAV-CAG-FRT-hM4DGi-tdTomato) viral vectors to neonatal homozygous 5HT3AR-Flpo mice. We confirmed using immunohistochemistry and multiplex fluorescent in situ hybridization a high degree of co-expression between Tomato mRNA with Htr3a mRNA and observed between 10-12% Tomato-immunoreactive (IR) neurons in lumbar dorsal root ganglia (DRG) for both viral constructs. Phenotypically, Tomato-IR colocalized with putative markers of A delta high threshold mechanoreceptors and silent nociceptors in the DRG. In thick tissue

sections (80 microns), we observed Tomato-IR neurites terminating as free nerve endings in hindpaw skin and throughout the knee joint including aligning the capsule, adjacent to menisci and within the synovium/fat pads. Optical stimulation of the hindlimb induced robust nocifensive responses and real time place escape avoidance in naïve 5HT3AR-Flpo mice transduced with ChrimsonR-tdTomato, but not control reporter only mice. Conversely, chemogenetic inhibition of 5HT3AR+ neurons reduced knee hyperalgesia in mice with knee inflammation induced by intra-articular administration of nerve growth factor. Based on these results, 5HT3AR+ sensory neurons may be major contributors to painful symptoms associated with knee osteoarthritis (OA) and therapeutic interventions that target these neurons may be beneficial. In ongoing studies, we are using in vivo calcium imaging in the DRG to characterize functional activation of 5HT3AR+ neurons in mice under naive conditions and following knee inflammation and post-traumatic OA. R21 AR07836.

Enkephalin in the Dorsal Raphe Nucleus Modulates Aversive Processing
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Chronic pain is a complex disease state associated with comorbidities such as depression, anxiety, and increased risk of suicide. It is important to understand the basic neurobiology behind the affective dysregulation of pain to effectively treat it. The endogenous opioid system can powerfully modulate both analgesia and motivational neural circuits and is therefore well-suited to modulate pain-induced affect. Dorsal midbrain nuclei such as periaqueductal grey (PAG) and the adjacent dorsal raphe nucleus (DRN) have been shown to be important sites of opioid action. The PAG is canonically associated with opioid-mediated descending pain inhibition and is desensitized during chronic pain states. The specific role of the DRN during chronic pain has not been characterized despite studies showing opioid activity here also modulating pain and motivated behaviors. To investigate the functional significance of DRN opioid signaling in pain sensitivity and related affective and motivational behaviors we disrupted preproenkephalin (PENK) in DRN using CRISPR-Cas9 in Penk-Cre mice. We found that CRISPR mediated knockdown of enkephalin peptide in the DRN enhanced inflammation-induced mechanical sensitivity and odor avoidance. Additionally, loss of DRN enkephalin diminished engagement with a novel social stimulus and odor preference. This attenuated reward/enhanced aversion phenotype is similar to behavioral changes observed in chronic pain states. Future studies will further investigate how this phenotype compares to chronic pain states and how DRN enkephalin contributes to affective dysregulation during chronic pain.

Understanding Chronic Bodily Pain Across Multisystemic Illnesses: A Comparative Analysis Using Exploratory Factor Analysis And Invariance Testing
Suvetha Ravichandran, Leonard Jason; DePaul University

Chronic pain is a debilitating symptom that often remains under-researched and poorly treated, particularly for those with multisystemic conditions. This study will explore the shared and distinct experiences of chronic bodily pain across four multisystemic illnesses: Myalgic

Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Multiple Sclerosis (MS), Post-Polio Syndrome (PPS), and Long COVID. Comparative analysis through exploratory factor analysis (EFA) and invariance testing will be used to examine commonalities and differences in underlying pain experiences for those with the above diagnoses as well as healthy controls based on their responses to pain items from the DePaul Symptom Questionnaire-1 (DSQ-1). A total of approximately 3,724 participants will be included: 2,403 with ME/CFS, 270 with MS, 242 with PPS, 299 with Long COVID, and 210 healthy controls. The data was collected from various countries, including the United States, Great Britain, Norway, Spain, Japan, and The Netherlands. Using this pre-collected data the following research questions will be answered: Do individuals with chronic illnesses (ME/CFS, PPS, MS, Long COVID) and healthy controls experience pain symptoms differently? How similar or different are the factors related to pain across these diagnostic groups? Exploratory factor analysis (EFA) will be used to identify latent structures in pain experiences for each of the diagnostic groups. Dependent on the results, invariance testing using multigroup confirmatory analysis or Procrustes analysis will be used to statistically compare the factor structures.

Accelerating Capsaicin Responses in Human iPSC-derived Nociceptors
Vincent Truong, Mariana Gavino, Patrick Walsh; Anatomic Incorporated

Nociceptors are critical for somatosensation, allowing the body to detect noxious chemicals or tissue damage. A hallmark for nociceptor identity has traditionally been functional responses to capsaicin, a chemical that agonizes the TRPV1 receptor leading to a sensation of heat or spiciness. Numerous groups have sought to manufacture capsaicin-responsive nociceptors from human pluripotent stem cells to provide a translational model for pain drug discovery, however this has proven difficult. These manufactured nociceptors either fail to develop capsaicin sensitivity at all, or require protracted time in culture.In this study, we have developed a novel directed differentiation methodology and culture system that promotes the development of nociceptors that robustly respond to physiological concentrations of capsaicin (100 nM) within only 3 weeks post-differentiation. These responses have been characterized by both multi-electrode array and calcium imaging. These nociceptors are expected to represent the most physiologically relevant translational pain model available, useful for drug discovery efforts to develop novel analgesics.

Human iPSC-Derived Sensory Neurons Reveal Pain Mechanisms in Fibrodysplasia Ossificans Progressiva
Hajira Elahi, Theodore Price, Patrick Dougherty; MD Anderson Cancer Center

Fibrodysplasia Ossificans Progressiva (FOP) is a rare and devastating genetic disorder characterized by progressive heterotopic ossification caused by a gain-of-function mutation in the ACVR1 gene. Alongside musculoskeletal anomalies, individuals with FOP often endure another persistent and debilitating challenge: excruciating pain. The rarity of FOP, coupled with substantial risks associated with invasive procedures to obtain patient specimens, has limited the

ability to comprehensively study the mechanisms underlying pain in this disorder. To address this gap, we generated induced pluripotent stem cells (iPSCs) from four unique FOP patients and differentiated them into sensory neurons (iSNs) with functional characteristics closely resembling those of human dorsal root ganglion neurons. These iSNs serve as a valuable and robust model for investigating the effects of ACVR1 mutations on sensory neuron function. Using whole-cell patch clamp recordings, we examined the physiological consequences of the ACVR1 mutation on baseline excitability and stimulus-evoked responses in patient-derived iSNs and compared these to wild type iSNs. This approach not only addresses a critical limitation in FOP research by providing non-invasive, scalable model systems to study FOP-pain, but also establishes a foundation for developing targeted therapies for pain management. These findings significantly enhance our understanding of the interplay between genetic mutations and sensory neuron dysfunction, underscoring the transformative potential of iPSC-based models in advancing research on rare genetic disorders.

From Biomarker to Mechanism: FGFR3 Autoantibodies in Painful Sensory Neuropathies
Lyuba Salih, Nicolas Dumaire, Liberty Francois-Moutal, Aubin Moutal, Christine Kim, Christian Moritz, Jean-Christine Antione, Jerome Honnorat; Saint Louis University

Antibodies targeting fibroblast growth factor receptor 3 (FGFR3) have been identified in patients with small fiber neuropathies (SFN), a group of disorders characterized by sensory neuron damage within the dorsal root ganglion (DRG) and associated with pain, paresthesia, and peripheral neuropathy. Although clinical evidence links FGFR3 autoantibodies to neuropathic pain, their specific role in sensory signaling and their direct contribution to pain mechanisms remain to be fully elucidated. Here, we demonstrate that FGFR3 autoantibodies bind to an extracellular epitope on DRG neurons, triggering neuronal hyperexcitability. Additionally, in vivo injection of FGFR3 autoantibodies into the paw of rats resulted in mechanical hypersensitivity. To counteract these effects, we designed synthetic peptides targeting the extracellular domain of FGFR3. These peptides effectively blocked the action of FGFR3 autoantibodies and prevented DRG neuron hyperexcitability. This finding highlights their potential as therapeutic candidates for autoimmune pain conditions. Our results suggest that FGFR3 autoantibodies play a direct pathological role in sensory neuronopathies by enhancing sensory neuron excitability and driving pain behaviors. Beyond their utility as biomarkers for SFN, FGFR3 autoantibodies may represent a primary driver of pain sensitivity in affected patients. Targeting FGFR3 autoantibodies or modulating their downstream signaling pathways offers a novel and promising strategy for the treatment of autoantibody-mediated neuropathic pain. Ongoing studies aim to further delineate FGFR3's role in sensory neuron signaling and its contribution to pain pathophysiology in autoimmune conditions.

Transcriptomic and Functional Characterization of Human Induced Pluripotent Stem Cell Derived Dorsal Horn Neurons As a Novel Tool for Pain Drug Discovery
Vincent Truong, Asta Arendt-Tranholm, Christian Petroski, Dong Liu, Sergey Grigoryev, Miaomiao He, Bob Petroski, Theodore Price, Patrick Walsh; Anatomic Incorporated

Advancing pain research has been hindered by the limited availability of human tissues, particularly dorsal horn neurons (DHNs), which are critical for understanding central pain mechanisms. Human induced pluripotent stem cell (hiPSC)-derived DHNs offer a near-limitless tissue source for these studies. Here, we present a scalable method to generate hiPSC-derived DHNs in just 7 days using directed differentiation with recombinant growth factors and small molecules, without the need for transcription factor overexpression. Following a three week maturation period, bulk RNA sequencing reflected a profile similar to primary human dorsal horn tissues. Immunocytochemistry confirmed a highly pure neuronal culture with a 70/30 ratio of glutamatergic to GABAergic neurons.We correlated this molecular data with time-course microelectrode array and whole-cell patch clamp electrophysiology studies that show the progressive maturation of these neurons. MEA studies of dorsal horn cultures showed a synchronous burst firing activity pattern as early as two weeks in culture, reflecting crosstalk between glutamatergic and GABAergic subpopulations. Using manual patch clamp, 72% of dorsal horn neurons showed resting membrane potentials below -50 mV, 86% firing spontaneous action potentials, and 57% generating spike trains with 1-second depolarizing current injection. Additionally, all neurons exhibited robust voltage-gated sodium currents (~3,000 pA), and 81% displayed miniature excitatory postsynaptic currents (mEPSCs), highlighting their functional maturity.These hiPSC-derived DHNs provide a reliable and scalable platform for studying pain mechanisms and offer significant potential for screening and identifying novel, centrally-acting analgesics.

The Cold Drinking Water Test: A Novel Behavioral Assay to Quantify Oral Cold Allodynia
Jennifer Ricano, Chloe Shudt, L. Savannah Dewberry, Andrea Nackley; Duke University Medical Center

Following oral surgery, up to 74% of patients experience temperature-dependent pain sensitivity, such as when consuming cold liquids or foods. In recent work, we demonstrated that mice undergoing oral molar extraction surgery and repeated swim stress exhibit evoked mechanical hypersensitivity at bilateral face sites as well as facial grimace. Yet, more functional assessments of pain remain to be examined. Thus, we sought to develop a simple clinically-relevant behavioral assay to quantify oral cold allodynia in mice. Separate groups of mice underwent the surgery + stress intervention or sham procedures. Mice were placed in individual cages for a 4-hour water deprivation period followed by a 1-hour period of ad libitum access to either room temperature or cold water, and differences in the volume of cold-water ingested measured. Our initial results show that mice undergoing the intervention consumed significantly less (~ 50% less) cold water on postoperative day 2 compared to those that underwent the sham procedures. This provides early indication of the utility of this new assay in evaluating orofacial pain which directly translates to that of a prevalent human pain experience. This work is ongoing, and we are currently assessing its efficacy compared to that of well-established orofacial pain assays, such as bite force and orofacial von Frey. With this work, we present a simple, sensitive behavioral assay that can be used to evaluate a clinically relevant pain symptom in awake, ambulating mice.

Chronic Alcohol Consumption Leads to Prolonged Recovery from Tactile Hypersensitivity in Mouse Models of Persistent Pain

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Chronic pain and alcohol use disorder (AUD) often occur comorbidly. Despite the high prevalence of chronic pain and AUD, little is known about the neural mechanisms underlying this comorbidity. In this study, we tested the hypothesis that chronic alcohol exposure disrupts recovery from mechanical hypersensitivity. Voluntary chronic alcohol exposure was performed using two-bottle free-choice paradigm and was paired with weekly mechanical threshold assessments via von Frey monofilaments. (1) Mechanical withdrawal thresholds significantly decreased in alcohol-drinking mice by weeks 4-5 compared to week 0 baselines and water-drinking controls. This withdrawal-associated hypersensitivity was attenuated by a selective inhibitor of spinal GABAA receptors. (2) In a model of acute inflammatory pain induced by unilateral intradermal hind paw injection of 3% capsaicin, alcohol-consuming males exhibited delayed and incomplete recovery of mechanical thresholds over a 24-hour period compared to water-consuming counterparts who recovered within this time frame. (3) Lastly, in a model of nerve injury-induced hypersensitivity using the sciatic nerve crush injury, water-drinking mice of both sexes recovered to pre-surgical thresholds after 4-5 weeks, while alcohol-drinking animals exhibited partial recovery at that time point. Immunohistochemistry on these brains suggested that alcohol-consuming nerve-injured mice displayed increased neural activation in regions relevant to reward and pain circuitry, namely the dorsal raphe nucleus (DRN). We are analyzing the activated neuronal subtypes and hypothesize that the activated DRN neurons are glutamatergic. Overall, these findings suggest chronic voluntary alcohol consumption prolongs the duration of recovery of tactile hypersensitivity after acute inflammatory pain and nerve injury-induced hypersensitivity models.

A Photochromic Controller for Reversible Regulation of Peripheral Opioid Analgesia

Luca Posa, Giovanna Romano, Carolyn Ji, Saif Khan, Bruno Paz, Gye Won Han, Antonina Nazarova, Saheem Zaidi, Vsevolod Katritch, Cornelius Gati, Dirk Trauner, Joshua Levitz; Weill Cornell Medicine

Although the mu-opioid receptor (MOR) is a primary target for managing moderate to severe pain, opioid treatments often lead to detrimental side effects that limit their use and may trigger opioid use disorders including fatal overdose. The widespread action of opioid agonists complicates the understanding of their circuit-level mechanisms and limits the ability to target specific receptor subpopulations, separating therapeutic benefits from harmful effects. In this study, we present a novel photoswitchable morphinan agonist, termed “azo-morphine-3” (AM-3), which reversibly shifts from low “trans” to high “cis” efficacy states (and vice-versa) when exposed to different wavelengths of light, allowing for optical modulation of MOR activity. Cryo-EM analysis of the two distinct “cis” and “trans” states of AM-3 bound to MOR reveals different binding modes of the photoswitchable azobenzene group, providing insights into the molecular determinants of agonist efficacy. In vivo, AM-3 enables precise, reversible optical

control of nociception in mice with fewer side effects due to its targeted action in peripheral tissues and localized activation at the pain site.

Characterization of the Spinal Projection Neuron Type Map of Somatosensory States
Satoshi Ishishita, Liliana Cano Gomez, Allan-Hermann Pool; University of Texas Southwestern Medical Center

Spinal projection neurons (SPNs) link the spinal cord (SC) to higher-order brain centers and are required for all central pain perception for tissue injuries below the neck. Both acute and chronic pain are centrally relayed by SPNs making them attractive therapeutic targets for pain management. However, the precise cell-type composition and specific molecular features of SPNs have remained ambiguous. To reveal the SPN repertoire, we first used spatial single-molecule transcriptomics to comprehensively characterize the cellular diversity within the intact SC. Our analysis revealed at least 110 anatomically and genetically distinct neuron types, exceeding previous estimates by several fold. Building on this, we performed cell type-informed retrograde viral tracing to map SPNs arborizing in higher-order brain centers implicated in pain processing. As a result, we identified 12 neuronal classes as SPNs (SPN1-12). Furthermore, we performed high-throughput stimulus-to-cell type mapping to characterize the responses of each SPN class to a diverse array of pain stimuli. We tested both superficial (thermal, mechanical, and inflammatory) and deep tissue (visceral, muscle, and joint) injuries, as well as non-noxious stimuli. This analysis revealed an SPN cell-type map of somatosensory states within the SC outlining the logic of SPN class tuning to individual tissue injury types. Our findings allow for a functional dissection of SPN classes in the regulation of supraspinal pain behaviors and inform therapeutic avenues to target this system for central pain control.

Clearing-Enabled Light Sheet Microscopy Imaging of Neuronal and Non-Neuronal cells in Murine Joints
Robin Vroman,Frank C. Ko1, Spencer Fullam, Delfien Syx, Eric Gracey, Dirk Elewaut, Fransiska Malfait, Richard J. Miller, Anne-Marie Malfait, Rachel E. Miller; Chicago Center on Musculoskeletal Pain

Clearing-Enabled Light Sheet Microscopy Imaging of Neuronal and Non-Neuronal cells of Murine JointsRobin Vroman, Frank C. Ko, Spencer Fullam, Delfien Syx, Eric Gracey, Dirk Elewaut, Fransiska Malfait, Richard J. Miller, Anne-Marie Malfait, Rachel E. Miller; Division of Rheumatology and Chicago Center on Musculoskeletal Pain, Rush University Medical Center , Chicago, ILMillions of people around the world suffer from chronic pain, creating a major healthcare load. Recent research highlighted the importance of non-neuronal cell types in musculoskeletal pain sensitization. Despite their importance, the spatial relationships and interactions between non-neuronal cells and pain-sensing neurons are still poorly understood, in part explained by the limitations of two-dimensional histology approaches. To address this, we developed a clearing-enabled light sheet microscopy approach for high-resolution 3D visualization and quantification of nerve density in murine tissues. Intact murine knee, ankle, and

shoulder joints from neuronal reporter mouse lines (Pirt-GCaMP3, NaV1.8-tdTomato) were decalcified and cleared using a modified DISCO protocol. Antibodies against tdTomato, GFP, or PGP9.5 stained nerves, while endomucin and podoplanin marked endothelial cells and reticular fibroblasts. Secondary antibodies in the red or far-red wavelengths were used to amplify signal. We imaged these samples with a Zeiss Lightsheet 7 microscope and using Imaris software we can visualize positively stained neuronal signal that is distinct from the non-neuronal labeled cells. Future work will focus on optimizing and applying these different co-stains on joints in disease models like osteoarthritis, Ehlers Danlos syndromes, or spondyloarthritis. Funding: NIH R01AR077019, P30AR079206, R01AR060364, R01AR064251, UC2AR082186.

Inflammatory Pain Effects on Melanocortin-4 and AMPA Receptors Expression are Modulated by Sex and Age

Andrea F Jones, Angela E Barattini, Queenie Wang, Jordan Roberts, Ella Milchan, Sydney K Long, Amanda R Pahng, Nicholas W Gilpin; Louisiana State University Health Sciences Center

Chronic inflammatory pain is more prevalent in females and increases with age. We previously reported that females injected with Complete Freund's Adjuvant (CFA) exhibit hypersensitivity and slower recovery than CFA-treated males. Also, expression of genes related to paw inflammation, triglyceride synthesis and nociception were modulated by age and recovery status. Melanocortin-4 receptor (MC4R) signaling is implicated in chronic pain by driving AMPA receptor insertion in the membrane. The goal of the current work was to measure CFA effects on MC4R and AMPA receptor expression in several brain regions important for pain in adolescent and adult male and female animals. Brains were harvested 3 or 11 weeks after CFA injection, central amygdala and periaqueductal gray (PAG) were punched and homogenized, then levels of MC4R, phosphorylated AMPA (pAMPA) and total AMPA were determined using Western Blots. There were no effects of CFA on pAMPA, pAMPA/AMPA ratio or MC4R protein levels in right CeA at either time point tested, but females exhibited higher levels of all three in right CeA compared to males at both timepoints. Additionally, pAMPA and pAMPA/AMPA ratio were higher in adolescents compared to adults at the late timepoint when nociception had returned to baseline levels in some but not all animals. Analysis of these proteins in the PAG is in progress. These data will inform planned future work that tests the effects of systemic and brain site-specific MC4R antagonists on pain-related outcomes in adolescent and adult male and female animals.Funding: VA Merit Review Award #I01 BX003451-01A1 (NWG).

Spinal Mechanisms of the Inhibition of Itch by Natural Cutaneous Stimuli

Abby Cui, Charles Warwick, Harrison Stratton, Richard Koerber, Sarah Ross; University of Pittsburgh

Chronic itch is debilitating for which we lack effective treatments. Itch can be robustly inhibited by various natural stimuli, such as scratch, cold, and topical menthol, however, we lack a population-level view of the neuronal populations that underlie such inhibition. To visualize spinal responses to cutaneous stimuli, we use 2-photon calcium imaging on ex-vivo skin-nerve

preparations where the skin, nerve, and the spinal cord are dissected in a continuum. Cell-type identification then can be achieved by Ca2+-coupled activity through drug activation (CICADA) in the presence of tetrodotoxin. To visualize both excitatory and inhibitory populations in the spinal cord, we express GCaMP8s or GCaMP6s pan-neuronally, identify inhibitory neurons by expressing Gad2-NLS-mCherry, and identify projection neurons by back-labeling from the parabrachial nucleus. The combination of neurochemical profiling and anatomical tracing not only allows us to visualize how responses to itch (induced by injection of compound 48/80) are influenced by cutaneous stimuli (such as scratch or cold), but also provide unprecedented amount of information about the identities of the neural populations involved. While previous literature suggests that during an itchy state, action potential is inhibited during and immediately after scratch in the spinal cord, we observed that scratch induces an increase of calcium events. Scratch induces different patterns of activity in excitatory and inhibitory populations, which provides valuable insights on the spinal logic of the inhibition of itch. NIH (R01NS096705 and R01AR063772).

Single Cell Sequencing Reveals Increased Expression of Trpm3 in CIPN Keratinocytes
Bradey Stuart, Anvitha Sriram, Vivien Blecking, Cheryl Stucky; Medical College of Wisconsin

Chemotherapy induced peripheral neuropathy (CIPN) is the primary reason for discontinuation of potentially lifesaving cancer therapy. CIPN manifests with both touch and cold evoked pain, as well as ongoing pain which occurs without stimulus. Paclitaxel (PTX) is often used in the management of various cancers, and between 60-90% of patients on PTX will develop CIPN. Previously our lab has shown that in PTX mediated CIPN keratinocytes contribute to the mechanical hypersensitivity (Mikesell, 2024). However, the mechanisms of ongoing pain in CIPN models are understudied. Given the role of keratinocytes in mediating noxious and innocuous touch, we conducted single cell sequencing of the hind paw and dorsal root ganglion (DRG) neurons in PTX treated animals. Analysis of the keratinocytes from this data set revealed an increase in the expression of the noxious heat, and spontaneous pain associated channel, Trpm3, without an increase in DRG expression. Furthermore, in vitro treatment of keratinocytes with PTX followed by calcium imaging revealed an increase in the number of responders to TRPM3 agonist, pregnenolone sulfate (PS). These results suggest a possible mechanism for mediating pain in CIPN, with tissue specific responses and a potential therapeutic target.

Eukaryotic Initiation Factor 2A Regulates Pain Hypersensitivity in Experimental Autoimmune Encephalomyelitis, a Model of Multiple Sclerosis
Brodie Woodall, Jonathan Iketem, Fishan Azad, Kree Goss, Theodore Price, Muhammad Saad Yousuf; University of Texas at Dallas

Multiple Sclerosis (MS) is an autoimmune disease of the nervous system characterized by neurodegeneration, demyelination, and inflammation. Over half of MS patients experience neuropathic pain that is poorly treated. We have previously shown that translation regulation contributes to pain pathogenesis, specifically through the Integrated Stress Response (ISR). The

ISR reduces protein synthesis via phosphorylation of eukaryotic translation initiation factor 2α (eIF2α). Under these conditions, eIF2A promotes the translation of stress-resistant genes such as ATF4 and BiP. By performing immunohistochemistry (IHC) on post-mortem DRGs obtained from MS patients, we demonstrate that p-eIF2α and eIF2A are increased in nociceptors of MS patients as compared to non-MS controls. To determine the effect of eIF2A in MS, we used the recently characterized global eIF2A-knockout (KO) mouse model in the murine experimental autoimmune encephalomyelitis (EAE) model of MS. We demonstrated that while eIF2A does not affect disease progression or total disease burden, eIF2AKO mice are protected from the development of mechanical and cold hypersensitivity. Bulk RNA sequencing of DRGs from eIF2AKO and WT mice at EAE disease onset identified enhanced interferon gamma signaling in WT DRGs while TNF signaling was increased in eIF2AKO DRGs. By using a mouse model of MS and human MS DRG tissues, our data establishes a translational approach to uncovering mechanisms of pain in MS and identifies potential avenues for therapeutic developments.

Breaking Barriers: Pain Studies in the Common Marmoset

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Chronic pain research predominantly relies on rodent models, but many promising targets identified in these studies fail clinical trials due to insufficient efficacy or translational relevance. To address this gap, there is a critical need for intermediary models to validate findings before human trials. This study explores the common marmoset (Callithrix jacchus) as a higher-order model for pain research, given their shared 93% genomic similarity with humans and analogous brain architecture, cognitive behaviors, and craniofacial anatomy, including temporomandibular joint (TMJ) and masticatory structures. We collected tongue, masticatory muscle, and trigeminal ganglia (TG) tissues to characterize sensory innervation using immunohistochemistry. TG neurons were further studied using calcium imaging for chemogenetic responses and patch-clamp electrophysiology for mechanical responses. Behavioral assays, including milk-enforced operant tasks, feeding behavior tests, and two-bottle capsaicin sensitivity tests, were developed to assess non-evoked orofacial pain in unrestrained marmosets. Our findings demonstrate that marmosets express nociceptor and non-nociceptor markers in a sex- and tissue-specific manner in the tongue and masticatory muscles. TG neurons responded to capsaicin in proportions comparable to humans and showed similarities and differences in mechanical sensitivity relative to mice. Early behavioral data suggest that marmosets can reliably model patient-reported pain symptoms in minimally invasive setups. These results position the common marmoset as a promising non-rodent mammalian model for bridging the translational gap between rodent studies and human clinical trials in chronic pain research.

Activation of Interleukin-1 Receptors Alters Mitochondrial Respiration and Signaling in the Dorsal Root Ganglia after Spinal Cord Injury

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Chronic pain develops in the majority of spinal cord injury (SCI) patients and is common in regions below the level of injury. This pain is refractory to medical intervention and negatively impacts quality of life. Our goal is to identify mechanisms underlying SCI-pain to find new therapeutic targets. We have found that below-level nociceptors become hypersensitive to mechanical and thermal stimulation and exhibit an increase in spontaneous firing. Whole transcriptome RNASeq of DRG from female mice 1 and 7 days following thoracic contusion injury revealed significant enrichment of transcripts related to IL-1b-dependent inflammation, while transcripts related to mitochondrial function and redox homeostasis were among the greatest suppressed post-SCI. IL-1b can affect neuronal function by altering mitochondrial respiration and function via activation of the IL-R1 receptor. Using Oroboros O2K fluorometry to measure mitochondrial respiration in the DRG, we found that SCI caused a significant decrease in respiration, which was rescued by conditional deletion of IL-1R1 from sensory neurons. IL-1b signaling can also alter mitochondrial respiration through activation of the cGAS-STING pathway. Additional analysis of RNASeq data showed that SCI also increases expression of transcripts in this pathway, while analysis of protein level showed an SCI-induced increase in STING in DRG. Collectively, these data suggest that SCI may increase nociceptor activity through an IL-1b-dependent activation of cGAS-STING that decreases mitochondrial function to promote pain.Funding: VA CDA1-1lK1RX003987, The Craig H. Neilson Foundation, the Kansas Institutional Development Award (IDeA) P20 GM103418, and P30 Ag072973.

Development of a G-protein Biased Peripherally Restricted Cannabinoid Receptor 1 Agonist

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The current opioid overdose epidemic highlights the urgent need to develop safer, more effective treatments for chronic pain. The cannabinoid receptor type 1 (CB1) is a promising non-opioid target for pain relief, but the therapeutic utility of CB1-targeted drug candidates has been limited by centrally mediated side effects like psychoactivity as well as reduced long-term effectiveness due to tolerance. We hypothesized that we could overcome both issues by designing peripherally restricted CB1 agonists that minimize arrestin recruitment. We achieved these goals by computationally designing positively charged derivatives of the potent CB1 agonist MDMB-Fubinaca (FUB). Our lead ligand, VIP36, is highly peripherally restricted and demonstrates efficacy in three animal pain models, with at least 50-fold dose separation between analgesic efficacy and centrally mediated side effects (e.g. cannabinoid tetrad effects). VIP36's efficacy was blocked by the peripherally restricted CB1 antagonist AM6545, indicating it exerts analgesic efficacy through peripheral CB1 receptors. VIP36 did not decrease in analgesic efficacy following repeated dosing.

Effects of Matrix Rigidity on Neuroinflammatory Glial Morphology, Function, and Epigenetic Programming

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Chronic pain regulation is influenced by the neuroinflammatory responses of microglia, which release pro-inflammatory mediators that alter neuronal function and disrupt pain regulation pathways. Matrix rigidity modulates microglial activation, amplifying inflammatory responses and contributing to altered pain signaling. This study examines how matrix rigidity affects microglial behavior, function, and epigenetic programming in vitro. BV-2 cells were cultured on 6-well plates with varying matrix stiffness to investigate the impact of mechanical properties on microglial function. Our results show that substrate biomechanics influence the area, circularity, and phagocytic capacity of BV-2 cells in response to matrix stiffness. Ongoing studies are exploring secreted factors and epigenetic modifications to further elucidate the molecular mechanisms driving these processes. These findings offer potential for biomarker discovery, therapeutic approaches, and treatment strategies for inflammation-related diseases, including chronic pain.

Histological Analysis Of Pain Processing Regions In Rats Following Closed Head Injury

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Traumatic brain injuries (TBIs) frequently cause somatosensory disabilities, with over 60% of cases leading to chronic pain. Mild TBIs (mTBI), such as concussions, are common in sports, military, and car accidents. Brainstem structures, particularly the periaqueductal gray (PAG), play a critical role in pain modulation and are vulnerable to mTBI-related forces, leading to maladaptive changes correlated with chronic pain. We hypothesize that histological alterations in inputs to the PAG, such as the anterior cingulate cortex and parabrachial nucleus, contribute to these maladaptive changes. This study used a weight-drop model of mTBI in female rats (CHI n=12; Sham n=12) to investigate pain-related behaviors and histological changes. Pain-like behaviors were evaluated for 35 days post-injury using Von-Frey filaments and Hargreaves' tests. Brains were collected on day 36 for immunohistochemistry. CHI rats showed sustained mechanical hypersensitivity compared to Sham rats ($p=0.0045$, ANOVA) but no significant thermal hypersensitivity ($p=0.1952$, ANOVA). Preliminary findings revealed no microglial overexpression in the PAG ($p=0.0671$, T-test). As an alternative approach, the microglial radius will be compared between groups as it is correlated with heightened microglial activation. Ongoing analyses are assessing markers for neuronal populations (NeuN) and plasticity (ERK-2). This research aims to clarify the mechanisms underlying pathological pain post-TBI, advancing our understanding of pain modulation in brainstem structures.

Chronic Pain Following Mild Concussive-like Injury: Development of a Rat Model
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Chronic pain, a frequent outcome of mild traumatic brain injury (mTBI), affects upwards 60% of patients. However, mechanisms underlying mTBI-induced chronic pain remain poorly understood, due to the lack of a reliable robust animal model exhibiting pathological pain following mild injury. This study aims to develop a rat model of mTBI-induced chronic pain to investigate the underlying mechanisms. A weight-drop model was used to induce closed head injury (CHI) in rats. Injury severity was evaluated using standard behavioral metrics—time to wake, time to right, and time to ambulate—to confirm the absence of loss of consciousness, aligning with mild injury criteria. Pain-related behaviors were evaluated measuring mechanical sensitivity with von Frey filaments and thermal sensitivity via the Hargreaves test. Behavioral assessments showed no significant differences between CHI and Sham groups in time to wake ($p=0.5250$, T-test), time to right ($p=0.7632$, T-test), time to ambulate ($p=0.6385$, T-test), confirming, the CHI model induced mild injury without loss of consciousness. CHI rats exhibited prolonged mechanical hypersensitivity compared to Sham rats ($p=0.0045$, ANOVA). However, no thermal hypersensitivity was observed. Ongoing experiments are validating injury severity using immunohistochemistry markers for microglia (Iba-1), astrocytes (GFAP), neuronal density (Neu-N), and neurofilaments (Nf-1) in the perilesional cortex and pain-processing regions. Future work aims to refine the model to enhance the pain phenotype and investigate neural plasticity changes in pain processing-related brain regions.These findings will provide insights into the mechanisms underlying pathological pain after closed head injury, contributing to the development of targeted therapies for mTBI-induced chronic pain.

Innovative Tissue Clearing And Immunostaining Technique For Mapping Neurofilament Positive Nerves In Rat Knee Joints
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Tissue clearing and subsequent light-sheet laser scanning of large-volume 3D specimens have become powerful tools for studying complex tissue architecture. Some of these 3D tissue clearing techniques include CUBIC, 3DISCO, iDISCO, and uDISCO, each refining the process for different applications and tissue types. In our interest to define how the neurons that mediate chronic joint pain innervate different joint tissues, we aimed to combine all tissue clearing protocols mentioned above to further improve its optical imaging quality and antibody compatibility compared to any specific protocol. Considering that Neurofilament (NF) proteins constitute a major intermediate filament component of the neuronal cytoskeleton, we used this biomarker for mapping tissue innervation of knee joints of twelve-month-old Wistar rats. Rats were cardiac perfused with 1X PBS and 4% paraformaldehyde (PFA). Hindlimbs were harvested, fixed (4% PFA) for 24h, decalcified in Immunocal, and cleared/immunostained with

our new technique. Tissue samples were imaged using a next-generation open-source light-sheet microscope (MesoSPIM). Our results showed successful detection of NF+ nerves in all knee joints analyzed, especially in the fat pad, patella tendon, meniscus attachments and the periphery of the knee. The cross-reactivity of NF antibody was confirmed in 2D knee tissue sections. In summary, this study presents an innovative 3D tissue clearing and immunolabeling protocol to analyze joint tissues. This approach will contribute to the development of new therapies to reduce the heavy burden of chronic joint pain in the future. This work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Funding: UC2AR082196.

Psilocybin Has No Analgesic Properties in Multiple Mouse Models of Acute and Chronic Pain

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The persistent difficulty in treating chronic pain has driven the exploration of alternative therapies, including the resurgence of interest in psilocybin. While studies showing the efficacy of single-dose psilocybin for depression have generated enthusiasm for the drug, evidence supporting its analgesic properties remains limited. We tested the hypothesis that psilocybin has analgesic properties using multiple mouse models of pain (complete Freund's adjuvant, acid-induced muscle pain, and spared nerve injury) at acute and chronic time points using a wide range of behavioral tests (Hargreaves, von Frey filament, muscle withdrawal threshold, marble burying, thermal place preference, and cold plate tests). We found no effect on hyperalgesia in any of these measures at any time point across multiple doses of psilocybin (0.3, 2, and 10 mg/kg), except for thermal place preference, which was better explained by psilocybin-induced hypothermia. No sex differences were observed in any of these measures. These results suggest that psilocybin does not have analgesic properties in multiple, diverse pain models and highlights the importance of thoroughly evaluating potential treatments, despite substantial enthusiasm for novel therapeutic mechanisms. Supported in part by a grant from the International Anesthesia Research Society.

Investigating The Role Of The α7 Nicotinic Acetylcholine Receptor In Myeloid Lineage Cells In Chronic Neuropathic and Inflammatory Pain

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Chronic pain is a maladaptive and increasingly prevalent condition. However, effective and safe treatment of pain remains one of the most significant challenges in medicine necessitating the investigation of new targets and approaches. Alpha 7 nicotinic acetylcholine receptors (α7-nAChRs) play an important role in pain and inflammation. We hypothesize that α7-nAChRs in myeloid lineage cells mediate an endogenous anti-inflammatory response. To study this, we engineered mice deficient in α7-nAChRs both globally and in myeloid cells and examined the role of these receptors in chemotherapy-induced peripheral neuropathy (CIPN) and acute and

chronic inflammatory pain. Spontaneous and evoked pain behaviors were measured along with other physiologic parameters and gene expression of pro-inflammatory cytokines in the nervous system. Mice deficient in α7-nAChRs in myeloid lineage cells had increased evoked pain behaviors and pathological aspects of CIPN and chronic inflammation and had an increase in gene expression of several pro-inflammatory cytokines in the peripheral sensory nervous system. α7-nAChRs in myeloid cells mediate an endogenous cholinergic anti-inflammatory pathway which is critical for the modulation of chronic neuropathic and inflammatory pain. Based on these findings, α7-nAChRs may be important targets for the development of novel therapeutic agents for the treatment of CIPN and chronic inflammation. Funding: NIH (1R01CA206028-01), NIH-NCI (P30 CA016059) and NIH-NIDA (P30 DA033934).

Role of IRE1A-XBP1 in Cancer Cell Co-Cultures with Macrophages and Sensory Neurons in CIPN Mechanisms

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Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of paclitaxel (PTX), manifesting as mechanical allodynia, thermal hyperalgesia, and tingling sensations. Here we show that PTX activates the IRE1α-XBP1 signaling pathway in immune cells, contributing to neurotoxicity. We developed an ex vivo co-culture system with sensory neurons, macrophages, and cancer cells, mimicking key aspects of CIPN. We hypothesize that inhibiting IRE1α-XBP1 can provide neuroprotection while enhancing PTX's anti-tumor effects. Using Endoplasmic-Reticulum Stress-Activated Indicator (ERAI) mice, which express green fluorescent protein upon IRE1α-XBP1 activation, we harvested bone marrow-derived macrophages (BMDMs) and dorsal root ganglion (DRG) neurons. We co-cultured BMDMs with MDA-MB-231 breast cancer cells to study their effects on DRG neurons. Cultures were treated with the IRE1α inhibitor MKC8866 or a vehicle (2.5 uM in 0.05% DMSO, 1 h), in the presence or absence of PTX (1 uM, 24 h). Neurite length and neuron counts were measured for neurotoxicity. Our results show that cells from ERAI mice are useful for visualizing IRE1α-XBP1 activation. PTX induced neurotoxic effects and IRE1α-XBP1 activation, and these effects were blocked by MKC8866 when neurons were cultured alone or co-cultured with macrophages or tumor cells ($P<0.05$ by t test). In our triple co-culture system, PTX or MKC8866 alone or combined showed neurotoxic effects ($P < 0.05$ by t test), indicating a complex tripartite interaction. We did not observe any overt effect on tumor cell counts. These findings highlight IRE1α-XBP1 inhibition to protect neurons from PTX-exposed macrophages and warrants further study to elucidate tumor interactions in our system.

First Steps in Elucidating a NaV1.8 Endocytic Complex Assembled by CRMP5

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The voltage-gated sodium channel NaV1.8 drives excessive sensory neuron firing in chronic

pain states. In a search for novel accessory proteins for Nav1.8, we identified Collapsin Response Mediator Response 5 (CRMP5), an axonal guidance protein, as a key regulator of NaV1.8 trafficking, controlling its internalization, degradation, or recycling. CRMP5 is expressed in dorsal root ganglia (DRG) neurons and binds NaV1.8 in the spinal dorsal horn and DRG. A peptide array revealed a 15-mer peptide in the first intracellular loop of NaV1.8 as the CRMP5 binding domain. CRMP5 knockdown increased NaV1.8 membrane localization, while overexpression decreased it. In sensory neurons, inhibition of the CRMP5/NaV1.8 interaction increased Nav1.8 membrane localization. Intraplantar injection of the blocking peptide induced mechanical hypersensitivity sensitive to the NaV1.8 inhibitor A-803467. Mechanistically, we found that CRMP5 regulates the assembly of an endocytic protein complex on NaV1.8 by recruiting E3 ubiquitin ligases to induce NaV1.8 internalization and followed by degradation. Conversely, CRMP5 competes with a deubiquitinase and therefore prevents the recycling of the channel. We used RNAscope to analyze the expression pattern of CRMP5, NaV1.8, two ubiquitin ligases and a deubiquitinase in our collection of male and female human DRG. Our findings position CRMP5 as a critical trafficking regulator of NaV1.8 fate at the membrane, acting as an adaptor for E3 ligases and a competitive inhibitor of deubiquitinase binding. This new insight into NaV1.8 regulation opens up potential therapeutic avenues for targeting the molecular mechanisms underlying chronic pain.

Arnica Ethanolic Extract Relieves Post-Operative Pain

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Post-operative pain is a medical condition in patients who undergo surgical procedures. Opioids are the most common choice for post-operative pain management. However, their use presents challenges such as tolerance, risk of addiction, and side effects like respiratory depression and constipation, which can significantly impact patient safety and quality of life. Therefore, there is a high demand for discovering effective and safe nonopioid drugs for managing post-operative pain. Arnica Montana (Arnica) is an herb that is traditionally used to treat trauma, inflammation, or tissue injuries. However, the analgesic effect of Arnica and the molecular mechanisms contributing to its activity on pain relief remains unclear. This study aims to unravel the therapeutic potential of Arnica ethanol extract and elucidate the molecular mechanisms underlying its ability to alleviate postoperative pain. In pursuit of this objective, CD-1 male and female mice underwent an incision on the left hind paw, and mice were treated with a gel containing 1% Arnica ethanol extract for one hour during the surgery and again 24 hours post-surgery, all while under anesthesia. The von Frey assay was performed to measure the mechanical threshold at different time points after the surgery. After the behavioral assay, the hind paw was harvested for Western blot to measure the protein expression. We found that topical treatment with 1% Arnica ethanol extract reduced the post-operative pain at different time points after surgery. The analgesic effect of Arnica ethanol extract may be contributed by activating Nrf2 and reducing Akt signaling pathways. These results provide a better understanding of Arnica as a medicine for pain relief.

Characterizing The Inflammatory And Behavioral Consequences Of Peripheral Nerve Injury

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Evidence from the peripheral nervous system and the spinal cord suggests that post-injury inflammation plays a critical role in the peripheral and central sensitization that initiates pain chronification. Supraspinal inflammation also occurs after peripheral injuries, but the significance of this inflammation to pain chronification is unclear. Using the Chronic Constriction Injury (CCI) model, we characterized prefrontal cortex inflammation after peripheral nerve injury in 18 male Sprague-Dawley rats. We hypothesized that the CCI would induce inflammation in the prelimbic and infralimbic cortices, with an accompanying increase in evoked mechanical allodynia (i.e., decreased mechanical force required for paw withdrawal) and spontaneous assessments of pain (e.g., reduced voluntary wheel running). Mechanical force tolerance was measured once weekly for 4 post-operative weeks using an Electronic Von Frey device, while changes in voluntary wheel running behavior were captured during once-weekly 24-hour recording sessions in PhenoTyper cages. A two-way mixed ANOVA of the average force required to induce injured foot withdrawal demonstrates that CCI induces chronifying neuropathic pain over 4 weeks post-injury, with CCI rats tolerating less force at each post-injury timepoint compared to Naïve rats (non-operative isoflurane-exposed controls, n = 12). Preliminary PhenoTyper data demonstrate a burgeoning stratification effect amongst our CCI cohort for wheel-running behavior. Further analyses with future cohorts will examine the possibility of CCI sub-phenotypes emerging via spontaneous behavior monitoring, underscoring the importance of pain behavior characterization beyond evoked pain behavior techniques like the Von Frey test. Funding: National Institute of General Medical Sciences R35 GM146774 (PI: Nyland).

Keratinocyte PIEZO1 Contributes to Pain and Impaired Wound Healing in Diabetes

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Diabetes mellitus is among the largest national health burdens, affecting 38.4 million people in the USA alone. Diabetes is a disorder characterized by sustained hyperglycemia, which leads to a variety of systemic complications- including painful diabetic peripheral neuropathy (DPN) and impaired wound healing[SA1] - that substantially diminish patients' quality of life. However, underlying mechanisms of painful DPN and impaired wound healing remain unclear. Keratinocytes make up ~97% of the epidermis and play a pivotal role in both wound healing and nociception. Our lab has identified keratinocyte PIEZO1 as a major contributor to normal mechanical sensation and mechanical hypersensitivity in a model of chemotherapy-induced peripheral neuropathy. Additionally, recent work has determined that keratinocyte PIEZO1 contributes to wound healing. Therefore, we hypothesized that sensitization of keratinocyte PIEZO1 contributes to painful DPN and impaired wound healing in diabetes. We assessed

PIEZO1 sensitization in keratinocytes isolated from diabetic patient samples, and mouse models of type 1 and type 2 diabetes by calcium imaging. Calcium transients in response to the PIEZO1 agonist Yoda1 were sensitized in both human and mouse diabetic keratinocytes. Additionally, deletion of keratinocyte PIEZO1 partially alleviated mechanical hypersensitivity in type 1 diabetic (T1D) mice. Keratinocytes from T1D mice exhibited reduced proliferative and migratory capacity compared to healthy controls. Further, application of Yoda1 decreased in vitro proliferation and does not further impair migratory capacity of keratinocytes isolated from diabetic mice. Altogether, these findings demonstrate that keratinocyte PIEZO1 may serve as a promising target for ameliorating mechanical hypersensitivity and impaired wound healing in diabetes.

Peritraumatic CRP Levels Predict Chronic Pain Development Following Traumatic Stress Exposure in a Sex-dependent Manner

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Background: Chronic pain following traumatic stress exposure (TSE) is common. Increasing evidence suggests that inflammatory/immune mechanisms are induced by TSE, play a key role in the recovery process versus development of post-TSE chronic pain, and are sex specific. In this study, we tested the hypothesis that, the inflammatory marker, C-reactive protein (CRP) , is associated with chronic pain after TSE in a sex-specific manner. Methods: We utilized blood-plasma samples and pain questionnaire data from men and women enrolled in AURORA, a multi-site Emergency Department (ED)-based longitudinal study of TSE survivors. We measured CRP using Ella/ELISA from 644 plasma samples collected in the ED (n=322) and six months following TSE (n=322). Repeated measures mixed-effects models were used to assess the relationship between peritraumatic CRP and post-TSE chronic pain. Results: Peritraumatic CRP levels significantly predicted post-TSE chronic pain, such that higher levels of CRP were associated with lower levels of pain over time following TSE, but only in men (men:b=-0.24, p=0.037; women:b=0.05, p=0.470). By six months, circulating CRP levels had decreased by more than half in men, but maintained similar levels in women (t(290)=1.926, p=0.055). More men with a decrease in CRP levels had decreasing pain over time versus women (men:83% women:65%; Z=2.21, p=0.027). Conclusions: In men but not women, we found that circulating peritraumatic CRP levels predict chronic pain outcomes following TSE and that resolution of CRP levels in men over time might be associated with increased pain recovery. Further studies are needed to validate these results.

Modeling Primary Sensory Neuron Senescence In Vitro

Lauren Donovan, Chelsie Brewer, Sabrina Bond, Riley Merkel, Vivianne Tawfik; Stanford University

Cellular stressors, such as aging or injury, can induce ‘cellular senescence’, a complex cell state which renders a cell unable to divide, resist apoptosis, and secrete a variety of pro-inflammatory

cytokines as part of their ‘senescence-associated secretory phenotype’ (SASP). Recently, we have identified neuronal senescence in the dorsal root ganglia (DRG) with age and following painful peripheral injury in vivo. Further, senescent neurons were found to be excitable and clearance of them improved pain outcomes following nerve injury in vivo. Here, we explored post-mitotic neuronal senescence in primary culture in vitro using young (3-months) and aged (24-months) mouse DRG, with/without prior nerve-injury. We found that aged uninjured primary sensory neurons displayed increased expression of senescence markers (p21/p16) compared to young uninjured neurons. Interestingly, previous nerve-injury did not enhance senescence marker, cytokine, or ATF3 expression beyond uninjured cultured primary sensory neurons, indicating that age was the biggest contributor to the senescence phenotype. We further assessed whether SASP factor and cytokine IL6, which is expressed by senescent DRG neurons, would alter electrophysiological properties of aged senescent DRG neurons in culture. Using whole-cell patch-clamp, application of IL6 was sufficient to increase the number of action potentials fired by senescent neurons. Overall, these in vitro data support previous data generated in vivo which identified enhanced senescence with age as well as heightened excitability of senescent neurons. Defining neuronal senescence and establishing neuronal properties in vitro will enable further investigation of therapeutically effective interventions which modulate or eliminate these particular cells to improve pain outcomes.

Heat Shock Protein-TRPA1 Axis Contributes To Episodic Pain In Fabry Disease

Jonathan Enders, Eve Prodoehl, Signe Penn, Anvitha Sriram, Cheryl Stucky; Medical College of Wisconsin

Fabry disease arises from mutations in the X-linked Gla and is the most common lysosomal storage disorder. Patients and carriers with Fabry disease frequently develop chronic pain and episodic pain crises, which are caused by fever, exercise, and even mild exposure to environmental heat. Relatively little is known about the mechanisms underlying episodic pain in Fabry disease, largely due to a dearth of preclinical models. We established the Fabry rat as the first preclinical model of episodic pain in Fabry disease by exposing them to transient, mild heat stress. Fabry rats and heterozygote female rats exhibited robust hypersensitivity to mechanical stimuli following mild heat stress, which largely recovered within 24 hours. Dorsal root ganglia (DRG) sensory neurons from Fabry rats exhibited heightened sensitivity to transient receptor potential cation channel A1 (TRPA1) agonists following in vitro heat treatment. Heat shock proteins (HSPs) normally confer resilience to heat and other cellular stressors but exhibited decreased expression in Fabry DRG neurons. To determine whether deficient HSP expression contributed to episodic pain in Fabry disease, we inhibited HSP70 and HSP90 in naïve DRG neurons, which sensitized TRPA1. Moreover, both exogenous HSP70 and HSP-amplifying pharmacological agents reversed TRPA1 sensitization in cultured Fabry DRG neurons and prevented heat-evoked episodic pain behaviors in Fabry rats. Thus, our findings establish the first model of episodic pain in Fabry disease. Moreover, we identify a novel regulatory mechanism for TRPA1 by HSPs and establish the heat shock response as a potentially valuable therapeutic target for pain in Fabry disease.

Mu Opioid Receptor Expressing Neurons In Spinal Cord Dorsal Horn And Rostroventral Medulla Differentially Regulate Nociception

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The mu opioid receptor (MOR) is expressed throughout pain regulatory regions of the central nervous system including the dorsal horn of the spinal cord (DH) and the rostroventral medulla (RVM). Opioid ligand-induced activation of MOR at these sites exerts potent analgesia. To better understand the function of neurons that express MOR, we tested the hypothesis that Oprm1Cre neuronal activity in the DH or RVM is sufficient to induce nociception. To test this, we injected AAV8-hSyn-hM4DGq or AAV8-hSyn-mCherry into the dorsal parenchyma of L4 DH or the RVM in Oprm1Cre mice, waited three weeks, induced chemogenetic activation with clozapine-N-oxide (CNO, 3mg/kg, i.p.), and then evaluated behavioral withdrawal responses to mechanical (von Frey), cool (acetone), and heat (hotplate) stimuli. We also determined performance on an accelerating rotarod as a test of motor coordination. We found that chemogenetic activation of spinal but not RVM Oprm1Cre neurons induced mechanical and cold sensitivity while neither induced heat sensitivity. With spinal Oprm1Cre, mechanical thresholds at 60 minutes were 1.1 ± 0.5 and 3.2 ± 0.4 grams after CNO and saline, respectively. Withdrawal duration in response to cold stimuli at 120 minutes were 7.1 ± 3.3 and 1.7 ± 0.4 seconds after CNO and saline, respectively. We observed no changes in motor coordination. These data indicate that activation of spinal but not RVM Oprm1Cre neurons causes nociception. Future studies will determine whether activation or inhibition of RVM Oprm1Cre neurons reinstates or prevents reinstatement of hyperalgesia, respectively, in models of latent pain sensitization.

Transdermal Optogenetic Technique Reduces Nociceptive Behaviors in an Acute Cystitis Mouse Model

Gabriella Robilotto, Rebecca Bornstein, Daniel Zelmanoff, Nia Dufeal, Ofer Yizhar, Aaron Mickle; Medical College of Wisconsin

This novel optogenetic technique is a noninvasive tool to understand neural pathways contributing to bladder pain. Traditionally, optogenetic silencing of these pathways remains challenging, especially when targeting bladder innervation. Other inhibitory opsins pose difficulties with prolonged inhibition, off-target effects, and require surgical implantation of fiber optics or wireless devices to activate opsins in freely moving animals. Here, we used a mosquito-derived homolog of mammalian encephalopsin/panopsin protein (OPN3), packaged into PHP.S, to inhibit neurotransmission in vivo with transdermal light, without surgical interventions. We hypothesize that transdermal light-activated PHP.S-OPN3-mScarlet will inhibit primary sensory neurotransmitter release and suppress nociceptive responses in mice with acute cystitis. We injected AAV PHP.S-hSyn1-OPN3-mScarlet intraperitoneally (IP) into neonatal mice for broad peripheral nervous system transduction. At twelve weeks of age, we performed baseline assessments with and without LED illumination. After inducing acute cystitis with cyclophosphamide, we repeated behavioral assessments. PHP.S-OPN3-mScarlet transduced mice spent more time in the LED-illuminated chamber after cystitis and had decreased abdominal sensitivity with LED illumination, suggesting nociceptive suppression. We expected PHP.S-

OPN3-mScarlet expression of the primary sensory neurons in the L6-S1 DRG, and the projections into the dorsal horn of the L4-L6 spinal cord. We found robust PHP.S-OPN3-mScarlet expression in the L6-S1 DRG and minimal expression within the spinal cord. This technique offers an optogenetic approach in vivo without surgical intervention to manipulate neural pathways.Funding: Rita Allen Foundation and NIHEB031249.

Validation Of An Intra-Bladder Optogenetic Device for Nociceptive Neuromodulation In TRPV1-Ai40 Mice

Hannah Anderson; Medical College of Wisconsin and Marquette University

Optogenetics involves the genetic expression of light-activated proteins (opsins) in neurons to modulate related neural cellular activity. In bladder research, optogenetics has been used to investigate the role of neuronal activity in bladder function. Effective light penetration of deeper tissue in freely moving animals has posed challenges in implantable device development. This work validates ~35 mm intra-bladder optogenetic devices wirelessly powered to emit green light (~575 nm) in vivo. We validate these devices using a mouse model that expresses archaerhodopsin-3 (ArchT) in TRPV1 lineage neurons (TRPV1-Ai40), primarily nociceptive sensory neurons. In this model, when activated with green light, ArchT inhibits the neural activity of these nociceptive neurons. The device base station is implanted subcutaneously in the upper abdomen, with the flexible light probe going through the abdominal muscles and sutured into the bladder lumen. We hypothesize that green light activation will activate ArchT in nociceptive neurons and decrease nociception and voiding frequency following cystitis. The device function is validated through behavioral assays conducted 7-14 days after implantation, including place preference and void assessment before and after cystitis induction via cyclophosphamide injections. Preliminary data (n=9) indicates device functionality, as bladder exposure to green light has resulted in improved patterns of voiding behavior both before and after cystitis induction and an increased preference for device activation following cystitis. This work demonstrates the utilization of optogenetics to manipulate specific neural functions in bladder physiology as a powerful tool for further research in pain, physiology, and optogenetics. Rita Allen Foundation, R21 EB031249.

Defining the Role of GRIK2 Kainate Receptor (KAR) in Peripheral Somatosensation

John Del Rosario, Jakayla Folarin-Hines, Hannah Crawford, Geoffrey Swanson, Robert Gereau IV; Washington University School of Medicine

Ionotropic glutamate receptors (iGluRs) are critical for excitatory neurotransmission in the central nervous system, specifically in neuronal and circuit maturation during brain development. Gain- and loss-of-function mutations in iGluRs genes have been shown to impair neuronal development. Reports have shown that an A657T pathogenic variant in the GRIK2 kainate receptor (KAR) gene causes neurodevelopmental deficits in humans, including developmental delay, speech delay, intellectual disability, ataxia, and hypotonia. Biophysical analysis of the ion channel kinetics shows a significant impairment of channel function represented by a decrease in

current amplitude, percent of desensitization, and slower kinetics of inactivation. In addition, electrophysiological recordings from mice harboring A657T mutations show an increase in action potential (AP) frequency in CA3 neurons, enhanced dendritic excitability, and decreased threshold for induction of LTP. Whether the GRIK2-A657T mutation also alters the peripheral nervous system and impairs somatosensation is not yet known. Recently, parents of individuals harboring A657T mutation reported that these individuals show profound sensory deficits denoted by a decrease in touch and pain sensitivity. My preliminary data, using a battery of behavioral tests, show that A657T mutant mice show a significant decrease in noxious cold and heat sensitivity, altered capsaicin response, and a profound decrease in touch sensitivity, thus suggesting GRIK2's crucial role in somatosensation. Therefore, understanding how aberrant GRIK2 signaling impairs somatosensation could help us propose new strategies to treat conditions that alter mechanosensation and promote chronic pain.Funding: K00NS113422.

300-Plex Spatial Transcriptomics Analyses of the Complete Set of Non-Opioid Orphan G Protein-Coupled Receptors in Clinically Relevant Human Dorsal Root Ganglion Neurons
Samay Shah, Matthew Sapio, Ofek Blivis, Gustavo Serrano-Berríos, Cole Saborio, Andre Ghetti, Dragan Maric, Michael Iadarola, Andrew Mannes; National Institutes of Health

This study was supported by the Intramural Research Program of the National Institutes of Health Clinical Center (ZIACL090034-09, ZIACL090035-08, ZIACL0033-09 to AJM), and of the National Institute of Neurological Disorders and Stroke (to DM). Supplementary funding was provided by the Office of Behavioral and Social Science Research, and from a Bench to Bedside Grant from the NIH Intramural Research Program to AJM. Research support was provided by the NIH Medical Research Scholars Program, a public-private partnership supported jointly by the NIH and contributions to the Foundation for the NIH from the American Association for Dental Research and the Colgate-Palmolive Company. AG is an employee and shareholder of AnaBios Corporation. The other authors have nothing to disclose.

Spinal Contributions Of Uridine Diphosphate-Glucose/P2Y14 Receptor Signaling In Neuropathic Pain In Rodents
Timothy Doyle, Silvia Squillace, Fatma Mufti1, Zhoumou Chen, Luigino Giancotti, Khiana Wilkinson, Ying Li, Janaine de Oliveira, Kenneth Jacobson, Kelly Karlage, Tally Largent-Milnes, Todd Vanderah, Jinsong Zhang, Peter Walter, Daniela Salvemini; Saint Louis University School of Medicine

The P2Y14 receptor (P2Y14R) has gained considerable traction as a possible target for therapeutic intervention in neuropathic pain states. Here, we show systemic administration of a potent and selective P2Y14R antagonists (PPTN) reversed behavioral hypersensitivities caused traumatic nerve injury, which was not blocked by naloxone. PPTN did not induce condition place preference or alter nociceptive thresholds in non-injured animals consistent with the lack of binding to opioid or cannabinoid receptors. Mass spectrometry revealed increased levels of the endogenous P2Y14R ligand uridine diphosphate-glucose (UDP-G) in rat cerebrospinal fluid at

time of peak behavioral hypersensitivities following CCI. Intrathecal (i.th.) injections of P2Y14R antagonists reversed behavioral hypersensitivities in mice with traumatic nerve injury; whereas, intrathecal injections of P2Y14R agonists recapitulated neuropathic pain behavioral phenotypes, identifying the spinal cord as a site of P2Y14R activity. The effects at the spinal cord are modulated by descending inhibitory projections from the RVM since an intra-RVM injection of PPTN also reversed allodynia. Unbiased transcriptomic analysis and pharmacological pathway targeting in the spinal cord indicate P2Y14R engaged pertussis toxin-sensitive (Gαi/o-linked) and MAPK-regulated pathways (ERK/p38) and neuroinflammation. In vitro studies further demonstrated P2Y14R inhibition attenuates microglial inflammatory cytokine expression. Our findings suggest that traumatic nerve injuries engage UDP-G/P2Y14R signaling in the spinal cord and the analgesic actions of P2Y14R antagonists involve inhibition of MAPK and neuroinflammatory signaling. P2Y14R may represent an innovative, non-opioid receptor target for neuropathic pain therapeutic development to address clinical needs. Funded by Saint Louis University start-up funds of Daniela Salvemini.

Opioid-Induced Axon Degeneration is Associated with Toll-Like Receptor 4
Trent Madden, Sarah Crowards, Andrea Chadwick, Gentry Totta-Griese, Lana Heslop, Will Hauser, Doug Wright; University of Kansas Medical Center

The pleiotropic effects of opioids have been attributed to activity at multiple locations and biochemical pathways within the nervous system. Although they canonically act through opioid receptors, studies have associated several adverse effects with activity at the pattern recognition receptor toll-like receptor 4 (TLR4). Recently, our preliminary data has shown that the addition of TLR4's prototypical agonist, lipopolysaccharide (LPS), to cultured mouse dorsal root ganglia neurons causes axon degeneration, suggesting that this is also a TLR4-dependent process. The decrease in mouse paw intraepidermal nerve fiber density (IENFD) following local subcutaneous injection of LPS supports this idea. Our preliminary data also show a reduction in distal leg IENFD in chronic pain patients with an opioid prescription compared to chronic pain patients without. To better understand the relationship between opioid use and axon degeneration, we are exploring the hypothesis that opioids cause axon degeneration in vitro and in vivo due to activity at TLR4. Ongoing experiments measure neuron growth parameters following treatment with morphine and its two most prevalent metabolites, morphine-3-glucuronide and morphine-6-glucuronide. To attribute findings to TLR4, drugs that cause axon degeneration will be tested in neurons from TLR4 null mutant mice and paired with LPS-RS (a TLR4 antagonist) in neurons from wildtype mice. Additional studies will measure axon degeneration following treatment in vivo and examine metabolic changes in vitro. This line of study may improve our understanding of TLR4's role in opioid adverse effects and provide evidence that axon degeneration is a component of these pathologies. Funding: R01NS043314-17, 5P20GM103418.

The Neuronal Membrane Proteasome (NMP) Expression is Modulated by Neuronal Activity to Regulate Pain Sensitivity
Emily Krueger, Eric Villalón Landeros; Loyola University Chicago

Neuropathic pain affects around 7-10% of the population, significantly impacting patients' quality of life, contributing to disability, psychological distress, and economic burden. Despite decades of research, the molecular mechanisms that regulate pain sensation remain poorly understood. Recently, we identified the neuronal membrane proteasome (NMP), a specialized proteasome localized on the plasma membrane of a subpopulation of somatosensory neurons that sense mechanical and pain sensation. This NMP mediates neuron-to-neuron communication to modulate pain sensitivity. However, the mechanisms that control NMP expression to regulate pain sensitivity are not understood. Here, we investigated the effects of neuronal activity on NMP expression and how this affects sensitivity to painful stimuli. Using dorsal root ganglion (DRG) neuron cultures, we hypothesized that hyperactive conditions drive the translocation of NMPs to the neuronal membrane and ultimately shape neuronal sensitivity to stimulation. We used surface biotinylation and antibody feeding techniques to measure NMP expression in response to sustained KCl stimulation. Then, we pre-treated DRG neurons to change NMP expression and used calcium imaging to measure neuronal sensitivity to stimulation. We found that sustained neuronal stimulation results in increased NMP expression and that increased NMP expression enhances neuronal sensitivity to painful stimuli. These data demonstrate that the NMP expression is dynamically regulated by the neuronal activity to modulate the sensitivity to subsequent painful stimuli. Taken together, these findings suggest that the NMP is a dynamic modulator of sensitivity to painful stimuli and a potential target for novel therapeutic strategies to manage pain.

MicroRNA Expression Changes Across Tissues And Time In A Rat Model Of Chronic Posttraumatic Pain

Alice Woolard, Lauren McKibben, Ying Zhao, Jacqueline Mickelson, Samuel McLean, Sarah Linnstaedt; The University of North Carolina at Chapel Hill

Chronic posttraumatic pain (CPTP) is a common outcome of traumatic stress exposure, yet few interventions are available to prevent/treat CPTP. Therefore, increased understanding of biologic mechanisms mediating CPTP pathogenesis is needed to inform the development of more effective preventive/treatment interventions. In the current study, we evaluated whether microRNA, small non-coding RNA with established roles in several pain disorders, are differentially expressed across tissues and time in the single prolonged stress (SPS) model, a well-validated animal model of enduring traumatic stress-induced hyperalgesia. To do this, we examined miRNA expression in ten tissues (hypothalamus, left and right hippocampus, amygdala, dorsal root ganglia, spinal cord, heart, muscle, whole blood, fat; n=6/group) at baseline and 2, 24, and 72 hours following SPS. High-throughput sequencing and DESeq2 analysis revealed differentially expressed ($\log_2|\text{fold change}|>1$ and $p<0.05$) miRNAs across all timepoints and all ten tissues. The greatest number of changes were observed in the blood and fat 2-hours post SPS. Specific miRNAs known to be involved in stress/pain, such as miR-34c-5p, miR-19a/b-3p and miR-200a/b/c-3p, were differentially expressed across multiple tissues, regionally, or in a tissue- and time-specific manner. Our findings highlight dynamic changes in microRNA expression across tissue and time following stress and implicate specific microRNA as potentially important to the pathogenesis of stress-induced hyperalgesia. Future studies are

needed to validate these results and determine mechanisms through which identified microRNA might influence CPTP development.

A Multiancestry Meta Genome-Wide Association Study of Migraine Among Men and Women Veterans Reveals Associations with Traumatic Brain Injury, Depression, and Post-Traumatic Stress Disorder.

Marianna Gasperi, Sara Brin Rosenthal, Adam X Maihofer, Armand Gerstenberger, Danniel Dochtermann, Saiju Pyarjan, Niloofar Afari, Caroline Nievergelt; VA Puget Sound Health Care System

Migraine is a neurovascular disorder prevalent in Veterans. Using Million Veteran Program and EHR data from over 433,010 participants across European (EUA; 278,768), African (AFR; 45,820), and Hispanic (HIS; 20,563) ancestral backgrounds, including 87,859 migraine cases, we conducted a multi-ancestry meta-analysis and post-GWAS characterization including replication, functional annotation, tissue enrichment, genomic structural equation modeling (GSEM), Mendelian randomization, and candidate drug analysis. The multi-ancestry meta-analysis revealed 36 GWS loci corresponding to 188 genes. Across all strata, we revealed 49 distinct loci - 13 with prior associations with migraine and 36 new to this study. Of the new loci, 29 were replicated nominally ($p<.05$) with previous migraine GWAS, mapping to 145 genes, including ASXL1, CELF4, and MAML3, which has been associated with chronic pain. Analyses revealed enrichment in brain tissues, including the frontal cortex, anterior cingulate cortex, nucleus accumbens basal ganglia, and the cerebellar hemisphere. We observed six loci specific to men, which may contain sex-specific signatures, including a locus associated with AHNAK. The observed scale heritability was estimated at 12% (SE: 0.006). The MVP population demonstrated increased polygenicity compared to previous cohorts, potentially indicating broader genetic contributions to migraine risk. GSEM revealed that despite the strong genetic correlations between migraine and TBI, PTSD, and MDD, only the association with TBI remains influential when modeling these conditions simultaneously. Further models revealed distinct yet correlated genetic architecture for migraine and six psychiatric disorders, emphasizing shared and unique genetic pathways among them. We identified several repurposing candidate drug targets, including metformin hydrochloride, targeting NDUFAF4.

Development and Characterization of a Genetically Diverse Mouse Model of Chronic Postsurgical Pain

Caitlyn Gaffney, Jeremy Thompson, Jeff Goff, Simon Haroutounian, Meaghan Creed, Andrew Shepherd; The University of Texas MD Anderson Cancer Center

Over 300 million major surgeries are performed worldwide, annually. Almost 20% of patients experience chronic postsurgical pain (CPSP), defined as new or worsened pain at the surgical site lasting for over 3 months after surgery. CPSP is manifested by heterogeneous peripheral and central mechanisms, which has contributed to the current gaps in prevention and management. Existing treatments are often applied indiscriminately, which does not take patient heterogeneity

into account. To better model the heterogeneity observed in patients, we have characterized a laparotomy model in genetically diverse UM-HET3 mice-a heterogenous stock produced by crossing CByB6F1/J hybrid females and C3D2F1/J hybrid males. These mice show substantial heterogeneity in peak pain sensitivity and duration of sensitivity following laparotomy, divisible into more 'resilient' and 'susceptible' sub-populations. There was considerable variability in animal performance in measures of locomotor activity and affective/cognitive function. Circulating inflammatory mediators associated with resilience or susceptibility to CPSP were also identified, and macrophage infiltration of skin adjacent to the incision was quantified. Our hope is that interrogating the molecular and cellular underpinnings of this heterogeneity will enable future efforts to identify pre-clinical correlates of CPSP in patients. This would improve forward translation of CPSP therapies by identifying CPSP patient phenotypes and symptoms that would be better captured by CPSP models, allowing for more personalized treatments.

Deep Brain Stimulation Of The Dorsal Anterior Cingulate Cortex Reduces Spontaneous Pain Behaviors In A Mouse Model Of Chronic Neuropathic Pain

Robert Graham, Hanyun Wang, Jacob Oscherwitz, Judith Golden, Meaghan Creed; Washington University in St. Louis School of Medicine

Over 30% of the United States' population is affected by persistent high intensity chronic pain that significantly diminishes patients' quality of life, with many patients not receiving sufficient pain relief from conventional therapeutics. Deep brain stimulation (DBS) is a possible therapy for patients with treatment resistant high intensity chronic pain. When applied to the dorsal anterior cingulate cortex (dACC), a key structure in the affective component of pain, DBS has been reported to reduce the aversiveness of chronic pain. Unfortunately, not all patients receive sufficient pain relief from dACC-DBS, and its therapeutic efficacy has been reported to wane over time. Currently, we do not understand the physiological mechanisms of dACC-DBS-induced pain relief, precluding the evidence-based innovation of the therapy to maximize pain relief in all patients. To address this gap, we developed a mouse model of dACC-DBS to elucidate the mechanisms of action of dACC-DBS-induced pain relief. In mice receiving the chronic constriction injury model of chronic neuropathic pain, dACC-DBS reduced the occurrence of spontaneous pain behaviors (e.g., licking, paw dorsoflexion, shaking or guarding the injured limbs). Using whole-cell patch clamp electrophysiology, we found that excitatory input from the medial thalamus onto subcortically projecting-dACC pyramidal neurons was decreased following chronic constriction injury. dACC-DBS significantly reduced inhibitory drive onto SC-dACC neurons, which would be hypothesized to restore the excitatory loop between the medial thalamus and dACC. These data lay the foundation for future studies that will optimize the dACC-DBS stimulation pattern to maximize the suppression of inhibitory action on SC-dACC neurons.

Signature of Intervertebral Disc Degeneration in a Mouse Model of Low Back Pain

Mohammed Alshagawi, Seunghwan Lee, Laura Stone; University of Minnesota

Low back pain associated with intervertebral disc degeneration (IVDD) is a major clinical challenge with limited therapeutic options. DNA methylation, which involves adding methyl groups to cytosine residues, typically silences gene expression. Previous studies demonstrated hypermethylation of the SPARC (Secreted Protein Acidic and Rich in Cysteine) gene in low back pain patients compared to controls, with an inverse correlation between SPARC methylation and RNA expression. In addition, treatment with demethylating agents effectively enhanced aggrecan mRNA expression in a mouse model of IVDD. However, genome-wide changes in methylation in degenerating IVDs remain unexplored. The goal of this study was to investigate epigenome-wide alterations in DNA methylation in genes and pathways associated with IVDD pathophysiology. Differential methylation was examined in IVD tissue from 8-month-old male SPARC-null and wild-type mice using the Infinium Mouse 250k Methylation BeadChip array. SPARC is crucial for extracellular matrix organization (ECM) and SPARC-null mice have accelerated disc degeneration and behavioral signs of low back and radiating leg pain. Methylation data were processed using the openSeSAMe pipeline. Enrichr web tool was used to conduct gene ontology analysis across biological processes, molecular functions, and cellular components. Significant methylation changes were observed in ECM (COL1A1, COL6A4, Lumican), inflammation (IL-6, IL-8, IL-13), signaling (WNT, CAMK2B, CAMK2D, and pain-related receptor (GRIA1) genes. Pathway analysis revealed enrichment in biological processes and molecular functions critical for disc homeostasis including extracellular matrix organization, inflammatory responses, and pain signaling pathways. These findings suggest a role for DNA methylation in IVD pathology and low back pain.

CELF Control of Post-Transcriptional Regulation in Persistent Pain

Madison Mueth, Peter Neufeld, Lindsey Fitzsimons, Eliza Grlickova-Duzevik, Benjamin Harrison; University of Maine

Persistent inflammatory pain is dependent on de novo protein synthesis in sensory neurons. Tissue damage promotes the release of inflammatory factors that enhance pain transduction through modulation of nociceptive ion channels, receptors, and neurotransmitters through signaling events within sensory neuron nerve endings and soma. Identifying post-transcriptional regulatory mechanisms that control the translation of nociceptive mRNAs may allow for successful modulation of sensory neuron sensitivity in persistent pain. Previously, we identified that the RNA-binding protein CUGBP Elav-like family member 4 (CELF4) is enriched in TRPV1-expressing sensory neurons in the dorsal root ganglia (DRG) and predicted that CELF4 preferentially associates with many transcripts of pronociceptive genes. Therefore, we generated conditional knockout (KO) mice with Celf4 deleted from distinct populations of adult DRG neurons to investigate its role in pain signaling. This revealed that Celf4 KO causes mouse sensory neurons to become extremely hyperexcitable compared to wild-type controls and these mice display robust mechanical and thermal behavioral hypersensitivities. Additionally, Celf4 KO induces an exaggerated response to low dose intraplantar NGF and capsaicin. We used RNA Immunoprecipitation sequencing and Translating Ribosome Affinity Purification sequencing to confirm CELF4 binding with nociceptive targets and assess changes in translational efficiencies of these targets under conditions of Celf4 KO. These studies revealed that CELF4 is a powerful negative regulator of sensory neuron excitability and behavioral sensitivities, and support

CELF4-regulated protein synthesis as a promising candidate mechanism that may be leveraged to control persistent pain. Funding: R01NS121533.

Knockout Of Neuronal MD-1 Increases Ly6G MRNA Cutaneous Expression And Mechanical Hyperalgesia In The Plantar Incision Model

Anjelina Fernandes, Hasita Ravula, Malavika Menon, James Jones, Kathryn Albers, Marsha Ritter; University of Pittsburgh

The role of sensory neurons in surgical wound healing, in particular nonpeptidergic neurons, is not well defined. A developing consensus is that activation of nonpeptidergic afferents that innervate barrier tissues, e.g., the skin, dampens an inflammatory immune response. Interestingly, analysis of sensory ganglia of mice that overexpress neurturin, a growth factor that supports the survival and growth of nonpeptidergic afferents, shows upregulation of immune-response genes, suggesting a role for these neurons in immune homeostasis and response to immune challenges. Towards understanding the role of nonpeptidergic neurons in immune signaling, a gene of interest is lymphoid antigen 86 (Ly86). We determined Ly86, which encodes myeloid differentiation 1 (MD-1), an innate immune response protein with anti-inflammatory actions, to be expressed in nonpeptidergic neurons. To examine the role of MD-1 in neurons, we used the mouse plantar incision model and tested if conditional knockout of MD-1 in MrgprD+ neurons impacts the immune response and incisional hypersensitivity. At 7- and 14-days post incision, mechanical sensitivity lateral to the incision was increased in knockout mice. We also determined that after 7d, RNA encoding Ly6G, a marker of neutrophils, was increased, correlating with the increased behavioral sensitivity. These data support the role of MD-1 and nonpeptidergic neurons as immune modulators in response to cutaneous injury and suggest possible adjunctive approaches to improve wound healing. Studies to uncover mechanisms that link cutaneous nonpeptidergic neurons, immune changes and hypersensitivity are continuing.

The Effect Of Naïve And Recombinant GABAergic HiPSCs And Exosomes In SCI Model Of Chronic Pain In Rats.

Stanislava Jergova, Behnaz Rahimi, Yelena Pressman, Lauren Kelly Tierney, Jacqueline Sagen; University of Miami

The Effect Of Naïve And Recombinant GABAergic HiPSCs And Exosomes In SCI Model Of Chronic Pain In RatsStanislava Jergova, Behnaz Rahimi, Yelena Pressman, Lauren Tierney, Jacqueline SagenUniversity of Miami, Miller School of Medicine, FloridaChronic pain following spinal cord injury (SCI) presents a therapeutic challenge, with disrupted GABAergic signaling and calcium-dependent release of pain-related neurotransmitters as key factors in pain development. The current study investigated the potential of recombinant GABAergic human induced pluripotent stem cells (hiPSCs) and their exosomes in the attenuation of SCI-induced chronic pain. hiPSCs differentiated into GABAergic neuronal cells and recombinant GABA/MVIIA cells were evaluated in the clip compression model of SCI pain in rats after spinal grafting. In separate groups, exosomal fractions were administered intravenously at several time

points post injury. Animals grafted with GABAergic hiPSCs exhibited reduced hypersensitivity, with a stronger effect observed in the GABA/MVIIA recombinant group, reversed by injections of anti-MVIIA or bicuculline. Early administration of exosomal fractions, followed by a booster, partially attenuated development of tactile hypersensitivity; stronger effects were observed with delayed injection of exosomes followed by several boosters. These findings suggest that recombinant GABAergic hiPSCs hold promise for managing chronic pain, and exosomal infusions may offer an additional strategy to attenuate pain development. Department of Florida of Health COPBC - University of Miami. The University of Miami and J.S. and S.J. hold rights to intellectual property used in the study and may financially benefit from the commercialization of the intellectual property.

Activation of TRPA1 and TRPM3 Triggers Ca2+ Waves in Central Terminals of Sensory Neurons and Facilitates Synaptic Activity in the Spinal Dorsal Horn
Alex Keyes, Yaroslav Andrianov, Charles Warwick, Leonid Shutov, Alexander Bassuk, Nana Voitenko, Pavel Belan, Yuriy Usachev; University of Iowa Carver College of Medicine

Transient receptor potential ankyrin 1 (TRPA1) and melastatin 3 (TRPM3) are transduction channels of sensory neurons that play major roles in peripheral mechanisms of somatosensation, including thermosensation, chemosensation and nociception. Recent studies suggest that both channels also contribute to central mechanisms of pain processing at the spinal cord level. TRPA1 and TRPM3 are highly permeable for Ca2+ suggesting that they could regulate Ca2+ signaling at spinal synapses. However, information about TRPA1- and TRPM3-induced Ca2+ signaling in the dorsal horn (DH) of the spinal cord is lacking. Here, we describe a dual-color technique for simultaneously measuring Ca2+ concentration ([Ca2+]i) in central terminals of sensory neurons and in spinal DH neurons by green (GCaMP3) and red (jRGECO1a) Ca2+ indicators, using two-photon imaging in isolated mouse spinal cord with attached dorsal roots (DR). DR stimulation elicited [Ca2+]i transients in axonal boutons of primary afferents and in cell bodies of DH neurons. The antagonists of AMPA and NMDA glutamate receptors, CNQX and AP5, inhibited [Ca2+]i transients in DH neurons, but not in sensory axonal boutons. Selective agonists of TRPA1 and TRPM3, ASP7663 and CIM0216, induced complex [Ca2+]i responses in distinct but partially overlapping subsets of sensory axonal boutons. Concomitant [Ca2+]i elevations were observed in DH neurons, which were blocked by CNQX and AP5. Patch-clamp recordings from DH neurons showed that ASP7663 and CIM0216 markedly enhanced excitatory synaptic activity. In summary, our findings suggest that TRPA1 and TRPM3 on central terminals of sensory neurons regulate presynaptic [Ca2+]i and synaptic transmission in the spinal DH.

Novel Therapeutic Actions of LSD1 Inhibition for Chronic Pain in Sickle Cell Disease
Ying He, Robert Molokie, Zaijie Wang; Midwestern University

Sickle cell disease (SCD) is an inherited blood disorder with debilitating pain as its hallmark feature. Previous studies indicated that inhibition of lysine-specific demethylase 1 (LSD1)

induced fetal hemoglobin (HbF) production and reduced disease pathology in a mouse model of SCD. The aim of this study was to determine whether LSD1 inhibition could alleviate persistent chronic pain in SCD. In a targeted knock-in mouse model of sickle cell anemia, we characterized ongoing spontaneous pain, as well as evoked hypersensitivity to mechanical and thermal stimuli using the conditioned place preference (CPP) paradigm, von Frey filaments assessment, and Hargreaves radiation heat test, respectively. Chronic treatment with RN-1 (2.5 mg/kg/day, i.p.,10 days), a selective irreversible inhibitor of LSD1, completely abolished clonidine-elicited chamber preference in SCD mice carrying human sickle hemoglobin, indicating the effective reduction of spontaneous affective pain component associated with SCD. Meanwhile, chronic RN-1 treatment significantly attenuated mechanical allodynia and heat hyperalgesia in mice with SCD, but not non-sickle control littermates. LSD1 inhibitor was involved not only in disease control, but also chronic pain reversal in SCD mice, implying the potential epigenetic anti-nociceptive mechanisms by LSD1 inhibition. These findings suggest the functional participation of LSD1 in the development of both non-evoke ongoing pain and evoked pain in SCD, which highlighted the possibility of a new intervention target to treat chronic pain in SCD.

Investigating The Electrophysiological And Transcriptional Properties Of Human Peripheral Sensory Neurons Using Patch-seq

Lite Yang, Jiwon Yi, Jun-Nan Li, Rakesh Kumar, Prashant Gupta, Adam Dourson, John Del Rosario, Allie Widman, Zachariah Bertels, Richard Slivicki, Maria Payne, Bryan Copits1, Robert Gereau; Washington University School of Medicine

Investigating the Electrophysiological and Transcriptional Properties of Human Peripheral Sensory Neurons Using Patch-seq Lite Yang, Jiwon Yi, Jun-Nan Li, Rakesh Kumar, Prashant Gupta, Adam Dourson, John Del Rosario, Allie Widman, Zachariah Bertels, Richard Slivicki, Maria Payne, Bryan Copits, Robert Gereau Washington University Pain Center and Department of Anesthesiology. Washington University School of Medicine, St. Louis, MO USANeurosciences Graduate Program, Division of Biology & Biomedical Sciences. Washington University School of Medicine, St. Louis, MO USA The human dorsal root ganglion contains diverse subtypes of peripheral sensory neurons. They exhibit distinct morphological, electrophysiological, and molecular properties, many of which may be modulated by one's life experience, such as pain history and opioid usage. However, the correlation of features across different modalities remains elusive. To address this, we developed a Patch-seq approach that combines patch-clamp electrophysiology with single-cell RNA sequencing, which enables us to simultaneously investigate the electrophysiological types (e-types) and transcriptional types (t-types) of human peripheral sensory neurons. Our analysis reveals a robust correlation between individual e-types to t-types, suggesting that distinct molecularly defined human DRG neurons have unique intrinsic and firing properties. In addition, we identified physiological and transcriptional features in individual neuronal populations that are associated with the donor's pain history. This study provides a multi-modal view of the human peripheral sensory neurons and may offer insights for developing novel targeted pain therapeutics.

Nociceptors Require SARM1 for Methylglyoxal-Induced Axon Degeneration
Gentry Totta-Griese, Jonathan Enders, Trent K. Madden, Lana L. Heslop, Will Hauser, Sarah J. Crowards, Douglas E. Wright; University of Kansas Medical Center

Diabetic peripheral neuropathy (DPN) is a comorbidity to diabetes that impacts millions of patients worldwide. DPN is associated with degeneration of peripheral nerves, leading to patients experiencing numbness, tingling, and pain. We hypothesize that methylglyoxal drives metabolic changes in nociceptors resulting in decreased NAD+ levels, SARM1 activation, and ultimately axon degeneration. Methylglyoxal is a glycolytic byproduct that is elevated in diabetic patients, and it has been proposed that methylglyoxal leads to pain in DPN via post-translational modifications on Nav1.8, provoking nociception. As an experimental model, we demonstrated that methylglyoxal causes mechanical allodynia one day after a single intraperitoneal injection (720ng). We now provide data that a single injection or application of methylglyoxal drives axon degeneration in vivo and in vitro. These results suggest that methylglyoxal could be an important link between pain and axon loss in neuropathy. SARM1 is an enzyme activated in axon degeneration, and NAD+, an abundant cofactor in many metabolic reactions, inhibits SARM1. Reduced NAD+ levels results in SARM1 activation. Methylglyoxal has been shown to induce metabolic adaptations through changes in mitochondrial membrane potential, ROS accumulation, and increased glycolysis. Here we tested whether nociceptors treated with methylglyoxal have decreased levels of NAD+ and SARM1 activation. Our experiments use genetic mouse models and pharmacological interventions to investigate if SARM1 is required for methylglyoxal-induced axon degeneration and how methylglyoxal mediates SARM1 activation. Understanding the relationship between pain and axon degeneration could lead to novel therapeutic targets or novel biomarkers to aid in diagnosing and treating DPN.

Treatment of C968 and CU1015 Prevents Chemotherapy-Induced Peripheral Neuropathy in Mice
Shaina Brown, Sid Sagna, Xin Chen, Liu Tuoen, Wei Lei; Manchester University

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting side effect of chemotherapy drugs that diminishes a patient's quality of life. However, common analgesics, such as opioids, have low efficiency for alleviating CIPN. Therefore, discovering new approaches to manage neuropathic pain is in high medical demand. Developing compounds with dual activity is an important approach to improving the therapeutic effects. Our studies demonstrate that Compounds 968 (C968) and CU1015, glutaminase inhibitors that have applications in cancer therapy, can also activate the nuclear factor erythroid 2-related factor 2 (Nrf2) signal pathway. This study aims to investigate the impact of C968 and CU1015 on the development of CIPN. CD-1 male and female mice received 4 doses of paclitaxel intraperitoneally and were concurrently treated with C968 or CU1015 intrathecally. The von Frey assay was performed to determine mechanical threshold before and after paclitaxel injections. We found that C968 modestly reduced the development of CIPN in both male and female mice. Interestingly, treatment of CU1015 has strong activity to attenuate the development of CIPN in male mice but no effect in female mice. The Western blots results indicated that treatment of

CU1015 promoted stronger activation of ERK & Akt in the spinal cord from female mice compared to that from male mice. Subsequently, cotreatment with either ERK or Akt inhibitors recreated the analgesic effect of CU1015 in the female mice. These findings suggest that compounds with dual glutaminase inhibition and Nrf2 activation could be future therapeutic agents for preventing CIPN in patients receiving chemotherapy drugs.

Mapping Microglia In The Brain After Nerve Injury Reveals Sustained Activity In Regions Encoding Affective Dimensions Of Pain

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Microglia are the resident macrophages of the central nervous system, regulating homeostasis through means including surveillance, phagocytosis, and soluble factor release. While historically categorized as either active or inactive, burgeoning research shows higher heterogeneity across microglial populations than previously appreciated. Microglial morphology operates on a spectrum, encompassing ramified, surveillant microglia which, upon detection of some insult, enter a reactive state typically characterized by a distinct, amoeboid phenotype. For example: after peripheral nerve injury, spinal microglia become reactive and begin releasing pro-inflammatory cytokines, initiating and maintaining pain. Similar microglial responses within the brain, however, have yet to be fully mapped. Here, we sought to elucidate microglial reactivity within the full brain, emphasizing regions associated with pain processing. We assigned sham or sciatic nerve constriction conditions to male and female Sprague-Dawley rats (N=6 per group, total N=48), using the chronic constriction injury (CCI) model for neuropathic pain. Whole brains were extracted at either 7- or 28-days post-injury. Brains were fully coronally cryosectioned then immunostained for CD11b. Using specialized software for automated analysis, we assessed morphological changes in microglia across the entire brain following nerve injury. Morphological assessment was cross-referenced with densitometry analysis. We observed morphological changes in microglia in brain regions involved in pain processing. While regions associated with sensory processing displayed transient microglial responses, regions involved in affective processing displayed sustained responses across the experimental time course. These data provide a rationale for investigating a possible differential role for microglia in affective and motivational versus sensory dimensions of neuropathic pain.

Prolonged Local Inhibition of the Neuronal Membrane Proteasome Results in Reduced Pain Sensitivity

Alexandra Peña, Taylor Church, Seth Margolis, Eric Villalon Landeros; Loyola University Chicago Stritch School of Medicine

The use of pan-proteasome inhibitors, such as those used for human cancer therapies, has been linked to development of painful peripheral neuropathy. Moreover, other studies suggest that low concentrations of these proteasome inhibitors result in reduced pain sensitivity leaving a gap in our understanding of the function of proteasomes in peripheral nerves. We recently identified the

neuronal membrane proteasome (NMP) in a subpopulation of somatosensory neurons whose activity is involved in mediating pain sensitivity acutely. Here we treat mice with intradermal paw injections of the NMP inhibitor, Biotin epoxomicin (BE), over 4 weeks and use behavioral assays to test for pain sensitivity as well as biochemical approaches to investigate nerve ending degeneration in paw skin of treated mice. We demonstrate that sensitivity to painful pinprick stimuli is reduced at 2 hours following injection of BE, and 1 week later this change in sensitivity returns to baseline. These results were consistently observed over 4 consecutive weeks of treatment with 1 injection of BE per week. We show that BE injected into the paw skin remains local and is not detectable in the sciatic nerve or spinal cord. Moreover, no nerve ending degeneration or sensorimotor behavior alterations were observed after 4 weeks of BE treatment. Taken together, these data demonstrate that local NMP inhibition using BE can transiently reduce pain sensitivity without causing nerve ending neuropathy or sensorimotor behavior alterations and point to the NMP as a therapeutic target for pain modulation.

TLR4 Deficiency Protects Against Inflammation and Neuropathy in a Diabetic Mouse Model

Sarah Crowards, Lana Heslop, Gentry Totta-Griese, Will Hauser, Trent Madden, Janelle Ryals, Douglas Wright; University of Kansas Medical Center

The most common complication of diabetes is diabetic peripheral neuropathy (DPN), characterized by pain, numbness, and tingling in the distal extremities caused by nerve degeneration. Despite its significant impact on patients' quality of life, understanding the mechanisms underlying DPN and developing effective treatments remains challenging. As a chronic inflammatory condition, diabetes involves the innate immune system receptor toll-like receptor 4 (TLR4), which has emerged as a key factor in several diabetic complications. TLR4 can be activated by various agonists associated with diabetes, triggering the production of inflammatory mediators. To uncover TLR4's role in diabetes complications, we induced diabetes using streptozotocin in TLR4 global knockout (TLR4-/-) and wild-type (WT) C57BL/6J mice. While genotype had no significant impact on weight loss ($p = 0.187$) or blood glucose levels ($p = 0.394$), TLR4-/- mice were protected against thermal hyposensitivity ($p = 0.004$) but not mechanical hypersensitivity ($p = 0.100$). Notably, diabetic TLR4-/- mice maintained intraepidermal nerve fiber (IENF) density comparable to their non-diabetic counterparts ($p = 0.841$), whereas diabetic WT mice experienced a significant loss of IENF density ($p = 0.024$). Furthermore, diabetic WT mice exhibited nearly higher dermal macrophage staining intensity than diabetic TLR4-/- mice ($p = 0.050$). WT diabetic mice also exhibited a marked increase in the inflammatory cytokine IL-6 ($p = 0.041$), a response absent in TLR4-/- mice ($p = 0.861$). Together, these findings reveal that TLR4 is a key driver of inflammation and neuropathy in diabetes, highlighting its potential as a therapeutic target for mitigating diabetic complications.

Chronic Optogenetic Spreading Depression Induces Changes in Meningeal Immunity

Talia Adi, Michael Gold; University of Pittsburgh School of Medicine

Despite recent approval of migraine therapies targeting calcitonin gene-related peptide (CGRP) and its receptor, successful management of migraine remains elusive for many patients. Because questions remain concerning the basis for therapeutic efficacy of these compounds, a better understanding of their mechanism of action may facilitate development of more effective treatments. There is evidence that meningeal immune cells may contribute to the initiation of migraine headache, and that CGRP receptors are present in a subpopulation of these cells. To test the hypothesis that immune cells contribute to the therapeutic efficacy of these drugs, we have assessed the impact of chronic cortical spreading depression (CSD) on immune cell density and phenotype in the meninges. Using a minimally invasive model of CSD, optogenetic spreading depression (OSD), OSD is evoked by blue light stimulation in Thy1-ChR2-YFP mice. After confirming blue light triggers OSD in these mice, we assessed immune cell numbers and phenotype with flow cytometry. Preliminary findings suggest that 14 days of OSD treatment in female mice shifts the proportion of immune cell subtypes in the meninges: myeloid cells are decreased, and lymphoid cells are increased. Ongoing experiments will assess immune cell phenotype and potential sex differences in response to OSD, as well as the impact of CGRP-targeting drugs. These experiments may not only reveal important immune mechanisms of migraine pathophysiology, but potential therapeutic effects of CGRP antagonists and novel immune targets for migraine treatment.

Machine Learning- Based Behavioral Analysis of Pain Related Behaviors Detects Changes Missed By Manual Scoring.

Anna French, Lindsey Preece, Luis Queme; University of New England

Traditional behavioral assessments for potential pain in rodents present several challenges, including inter-investigator variability, problems with reproducibility, and investigator bias. Recent advances in computer vision and deep learning allow the detection of rodent behaviors in a more natural context and within a higher timescale resolution that is often imperceptible to the human eye. Our laboratory performed a series of traditional pain-related behavioral tests and paired this with analyses using a Blackbox One machine that utilizes near-infrared (NIR) cameras and weight-sensing Fourier transform infrared (FTIR) sensors to visualize and analyze voluntary rodent behavior with limited human interference. We hypothesized that mice with hind limb ischemia with reperfusion (I/R) injury would display pain-related behaviors in traditional tests that would correlate to Blackbox outputs. Male and female mice exposed to an I/R injury were tested using traditional and Blackbox behavioral tests at Baseline and on days 1, 5, and 8 post injury. On day 1 post injury there was an increase in guarding and a decrease in mechanical withdrawal thresholds as well as grip strength. This was correlated with a decrease in hind paw luminance and an increase in hind paw lifted time in the Blackbox measurements. Guarding, grip strength, and withdrawal thresholds returned to baseline levels by day 8 post-injury, while the Blackbox measurements remained at day one levels and did not show signs of recovery after the injury. These findings suggest that computer vision methodologies enhanced by IR vision may detect ongoing behavioral changes that are not captured by traditional scoring.

Mouse Models of Non-Dystrophic and Dystrophic Myotonia Exhibit Nociplastic Pain-like Behaviors

Tyler Nelson, Aida Calderon-Rivera, Paz Duran, Kimberly Gomez, Santiago Loya-Lopez, Rajesh Khanna; University of Florida College of Medicine

Mouse Models of Non-Dystrophic and Dystrophic Myotonia Exhibit Nociplastic Pain-like Behaviors Tyler S. Nelson, Aida Calderon-Rivera, Paz Duran, Kimberly Gomez, Santiago Loya-Lopez, Rajesh KhannaDepartment of Pharmacology and Therapeutics, University of Florida, Gainesville, FL 32610, USA Pain is a debilitating symptom in myotonic disorders, yet its mechanisms remain poorly understood. This study evaluated pain-like behavior in murine models of pharmacologically induced myotonia and myotonic dystrophy type 1 (DM1). Impairment of the CLCN1 gene, encoding skeletal muscle voltage-gated CLC-1 chloride channels, reduces chloride ion conductance in skeletal muscle cells, causing prolonged muscle excitability and delayed relaxation. We used the CLC-1 antagonist anthracene-9- carboxylic acid (9-AC) and HSA LR20b DM1 mice to model CLC-1-induced myotonia. Experiments included in vivo pain behavior, ex vivo calcium imaging, and whole-cell current-clamp electrophysiology in mouse dorsal root ganglion (DRG) neurons. A single 9-AC injection induced myotonia and allodynic pain-like behavior, while HSA LR20b mice displayed allodynia and hyperalgesia. Interestingly, despite these pronounced pain-like behaviors, DRG neurons did not exhibit hyperexcitability in either model. These findings suggest that myotonia induces nociplastic pain through central sensitization rather than peripheral mechanisms. This study offers valuable insights into the pathophysiology of pain in myotonic disorders, emphasizing the utility of myotonic mouse models for exploring pain mechanisms and evaluating novel analgesics. Future research should prioritize uncovering the central mechanisms driving myotonia-induced pain and developing targeted therapies to alleviate this significant clinical burden. Funding: K00NS124190 and a Development Grant from the American Neuromuscular Foundation (to TSN). RF1NS131165, R61NS126026, and R01NS120663 (to RK).

Neuropathic Pain-Related Adaptations in Accumbal-Projecting Mesolimbic Dopamine Neurons

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Mood disorders are commonly associated with chronic pain (CP) and present additional treatment challenges, however the mechanisms underlying this link are not well understood. Decreased activity of dopamine neurons in the ventral tegmental area (VTA) leading to a hypodopaminergic state is thought to be mechanistically linked to development of a negative affective state, however direct evidence for this is lacking. In addition, the VTA is a heterogeneous region with multiple dopaminergic projection targets, each of which plays a unique role in reward processing. The projection to the nucleus accumbens core (VTA->NAc) is involved in positive reward prediction error, but it is unknown if CP-related alterations in its activity lead to an amotivational state. We hypothesized that VTA->NAc neuron activity is decreased at a chronic timepoint following spared nerve injury (SNI)-induced neuropathic pain,

and that this correlates to impaired performance on a reward-based operant task. Using ex vivo patch clamp recordings, we found that action potential firing of VTA-> NAc neurons is reduced 5 weeks following SNI due to earlier entry into depolarization block. We then characterized pain-related changes in activity of small conductance calcium-activated potassium (SK) channels and the M and A type currents, which are critical regulators of action potential firing in VTA->NAc neurons. These electrophysiological changes correlated with reduced reward motivation on a reward-guided decision-making task. These results suggest that impaired VTA->NAc activity correlates with CP-related amotivation and supports development of therapeutic strategies to address these deficits for treatment of CP-related affective disorders.

TRPM8 Signaling in Human DRG Neurons

Matias Preisegger, Christopher Scott, Brian Davis, Michael Gold; Department of Neurobiology, University of Pittsburgh School of Medicine

The transient receptor potential melastatin 8 (TRPM8) ion channel is essential for the transduction of cooling stimuli and mediating responses to cooling agents like menthol. In rodents, TRPM8 is expressed in two distinct sensory neuron subpopulations: a small subset defined by TRPM8 expression alone and another co-expressing TRPM8 with CGRP and TRPV1. This distribution highlights TRPM8's roles in cooling sensation and cold hypersensitivity, commonly linked to neuropathic pain. Although RNA-seq data suggests comparable TRPM8 expression patterns between rodent and human dorsal root ganglion (DRG) neurons, functional analyses in human DRG neurons remain limited. This gap limits our understanding of TRPM8's role in cold hypersensitivity and pain management, hindering the development of targeted therapies.Using fura-2-based calcium imaging, we examined dissociated human DRG neurons obtained with next-of-kin consent. Neurons were challenged with (-) menthol at various concentrations and capsaicin (300 nM) using a rapid drug exchange system. Cooling stimuli were applied in separate experiments, reducing temperature from a holding temp of 35°C to 10°C in 5°C steps.Preliminary results suggest that 30 μM is a saturating concentration of methol, generating a Ca2+ transient in ~16% of neurons, with notable inter-donor variability. Of these, 85% also responded to capsaicin. Higher menthol concentrations (>100 μM) induced responses in >50% of neurons. Two distinct cold-responsive neuronal populations were observed, including transient and sustained responders. Additionally, cold responses were observed in a subpopulation of satellite glial cells.Single-cell sequencing is underway to characterize gene expression patterns in menthol- and cold-responsive neurons and investigate donor variability.

A Novel System For Micro-Mechanical Stimulation Of Sensory Neuron Axons In Microfluidic Devices.

Spencer Fullam, Dongjun Ren, Abdelhak Belmadani, Daniel Hoffman, Richard Miller, Anne-Marie Malfait, Rachel Miller; Rush University Medical Center

Microfluidic cell culture devices allow for the separation of neuronal cell bodies from the nerve terminals and are increasingly used to study neuronal growth, interaction with other cell types,

and responses of receptors expressed at the terminals. However, the small dimensions of microfluidic devices make it challenging to apply localized mechanical stimuli to the neuronal axons—key for investigating mechanosensitive sensory neurons like nociceptors and proprioceptors. We developed and validated an affordable system to apply precise mechanical strain to hydrogels using a Xona Microfluidics® co-culture chip. Our system integrates a stepper motor, 3D-printed base, Arduino, battery, control buttons, enclosure, metal plate, and spring. The motor compresses the spring, applying force to a hydrogel within the chip. Using a jig, 1% agarose hydrogels (11 mm × 2 mm × 7 mm) were cast, and motor steps were calibrated to achieve specific strain levels. Strain thresholds for hydrogel failure were also determined. Dorsal root ganglion (DRG) neurons were isolated from (8 weeks old, male, NaV1.8-tdTomato) mice and cultured for five days in the Xona chip, during which time axons grew through the 7 µm-wide channels and into the hydrogel chamber. Calcium imaging was performed using Calbryte 520 AM (5µM) to assess mechanosensitivity. Upon hydrogel compression, 3.7% of DRG cell bodies responded to 35% strain, while 9.3% responded to 39% strain. This <$100 system provides a practical tool for researchers investigating mechanotransduction. All design files, part lists, build instructions, and software will be freely accessible on protocols.io. Funding: NIH R01AR077019, P30AR079206, R01AR060364, R01AR064251, T32AR073157.

Exploring the Role of Descending Dopamine Pain Modulation in the Transition to Chronic Pain

Angela Smith, Elizabeth Gross, Kazuhiro Hayashi, Adam Janowski, Stephanie Gantz, Kathleen Sluka; University of Iowa

Descending pain modulation systems are key targets in understanding the transition to chronic pain. The descending dopamine pain modulation system originates in the A11 nucleus of the hypothalamus and projects ipsilaterally to the spinal cord. Very little is known about the activity and properties of A11 dopamine neurons in the context of chronic pain. However, in animals with an inflammatory hyperalgesic priming model, spinal dopamine and dopamine D1-like receptors have been implicated in the transition to chronic pain. We hypothesize that A11 neurons are active in the transition to chronic pain, releasing dopamine in the spinal cord and facilitating hyperalgesia via D1-like receptor mediated phosphorylation of NMDA receptors. In male and female C57 mice we used a noninflammatory hyperalgesic priming model consisting of two spaced injections of acidic saline; the first injection is a priming stimulus, while the second injection initiates a transition to chronic pain. We collected brain and spinal cord tissue from animals with and without pain to characterize A11 dopamine neurons and spinal dopamine in the context of chronic pain. We also evaluated the effect of pharmacological manipulation of spinal D1-like receptors during the transition to chronic pain. We found that in this model, spinal D1-like receptor blockade delays the onset of hyperalgesia in male but not female mice. Additional experiments will characterize the activity and properties of A11 dopamine neurons, the source of spinal dopamine. Future directions will explore if spinal D1-like receptor activation mediates phosphorylation of NMDA receptors. Funding: NIH AR073187, T32NS045549, R37DA060149.

Antinociceptive Effects of Speciogynine, Paynantheine, and Their 9-O-desmethyl Metabolites.

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Products derived from the kratom plant have shown clinical potential in the treatment of pain, opioid withdrawal and opioid use disorder. Although kratom has not been approved for medicinal purposes in the United States, preclinical studies demonstrate several therapeutic effects of kratom extracts that are consistent with reports in humans. Kratom leaves contain over 45 alkaloids, and each alkaloid has unique pharmacological characteristics. In this study, the kratom alkaloids speciogynine (SPG) and paynantheine (PAY) and two of their metabolites, 9-O-desmethylspeciogynine (des-SPG) and 9-O-desmethylpaynantheine (des-PAY), were assessed for their antinociceptive properties in C57BL/6 mice using the hot plate assay. Both SPG (10 mg/kg) and PAY (17.8 mg/kg) produced antinociception 30 minutes after intraperitoneal administration. Intrathecal (IT) SPG (10, 17.8, 32 μg) produced antinociception in the hot plate assay 10 minutes after administration and was diminished after 30 minutes, whereas des-SPG did not. IT PAY (5,6, 10, 17.8, 32 μg) produced antinociception 10 minutes after administration and was diminished after 30 minutes. The metabolite des-PAY (17.8, 32 μg) also produced antinociception 10 minutes after IT administration, which was diminished after 30 minutes. Neither 5-HT1A nor a2-adrenergic receptors contributed to the antinociceptive effects of SPG, PAY, or des-PAY as co-administration with either WAY-100635 or yohimbine did not decrease latency to respond to thermal stimuli. These results provide insight into differences in the behavioral pharmacology of two parent kratom alkaloids and two of their metabolites.

CRISPR Epigenome Editing of IL1R1 Expression Reduced Osteoarthritic Cartilage Induced Sensory Neuron Sensitivity to Thermal Stimuli

Joshua Stover, Alejandro Almarza; University of Pittsburgh

Osteoarthritis (OA) of the knee and temporomandibular joint (TMJ) can lead to painful joints containing inflammatory cytokines, that may contribute to OA pain by sensitizing nociceptive neurons to non-painful stimuli. To test this hypothesis, we measured neuron responses of dorsal root ganglia (DRG) and trigeminal (TG) neurons seeded on OA and healthy cartilage. Rat DRG and TG neurons were isolated and seeded upon OA cartilage from patients undergoing total knee replacement (cadaver tissue used as control). Neurons were loaded with calcium dye and calcium transients were imaged during thermal stimuli. The percentage of TG neurons seeded on OA cartilage exhibiting calcium transients was significantly elevated over controls. Similarly, the percentage of DRG neurons seeded on OA cartilage were significantly elevated over controls. Next, we investigated the ability of CRISPR epigenome editing vectors to regulate inflammatory cytokine receptor expression in TG neurons. When TG neurons were transduced with CRISPR epigenome editing vectors (dCAS9-KRAB) targeting the IL1R1 gene promoter, the expression of IL1R1 was significantly downregulated compared to TG neurons transduced with non-targeting control vectors. Finally, we demonstrated the ability of IL1R1 epigenome editing of TG neurons to regulate OA cartilage induced neurons sensitization. IL1R1 epigenome edited TG neurons

seeded on OA cartilage exhibited significantly reduced heat induced calcium transient response (DF/F) when compared to non-target edited TG neurons seeded on OA cartilage. These results suggest IL-1B signaling in OA cartilage may contribute to neuron sensitization and further suggest that CRISPR epigenome editing IL1R1 is a potentially treatment strategy for OA pain.

Bioenergetic Regulation of Signaling in Nociceptors Using Mouse and a Human Sensory Neuron-Derived Cell Line

Jacquelyn Ames, Emily Addleson, Ivan Bonet, Jon Levine, Derek Molliver; University of New England

The transition to chronic pain is associated with metabolic remodeling in dorsal root ganglion (DRG) neurons, including glycolytic activation and diminished mitochondrial respiration. Pyruvate dehydrogenase (Pdha1) serves as a key rheostat for the Krebs cycle and regulates mitochondrial respiration. Pdha1 is inhibited through phosphorylation by Pdha1-selective kinases (PDKs), and Pdha1 inhibition has been implicated in nociceptor sensitization. Consistent with this hypothesis, we found that Pdha1 phosphorylation was enhanced in response to hindpaw injection of capsaicin or carrageenan in mice, and intrathecal Pdha1 antisense delivery in rats induced hyperalgesic priming. PDK inhibitor dichloroacetate has been proposed for the treatment of glycolytic acidosis and pain but causes peripheral neuropathy, likely through mitochondrial hyperpolarization, reactive oxygen species production, and excessive mitochondrial calcium uptake. In contrast, mitochondrial uncoupling drug BAM15 suppresses mitochondrial hyperpolarization and is antinociceptive in a range of behavioral models. In mouse DRG neurons and the HD10.6 human DRG-derived cell line, BAM15 (2μM) reduced mitochondrial membrane potential and rapidly dephosphorylated Pdha1 in a dose-dependent manner, enhancing mitochondrial respiration measured by Seahorse assay. PDHA1 phosphatase activity is enhanced by increased cytosolic calcium, but BAM15-induced dephosphorylation was unaffected by the calcium chelator BAPTA-AM. PDKs are inhibited by the Pdha1 substrate pyruvate and by ATP depletion. However, inhibition of the mitochondrial pyruvate transporter with UK5099 (5μM) did not prevent BAM15-induced PDHA1 dephosphorylation, and cellular ATP levels were minimally reduced by BAM15. Overall, we find that BAM15 is antinociceptive and causes PDHA1 dephosphorylation in mouse and human DRG-like cells while preventing deleterious mitochondrial hyperpolarization.Funding: R01NS13157.

B Cell Contributions To Pain Behaviors And Autoantibody Accumulation Following Neuropathic Injury

Kat Propsom, Benjamin E. Gourley, Samantha T. Woodke, Michael J. Lacagnina; Cincinnati Children's Hospital Medical Center

Neuropathic pain results from an injury or damage to the somatosensory nervous system and affects approximately 7-10% of adults. Neuroimmune interactions are considered critical for the development and maintenance of neuropathic pain, but the precise mechanisms remain unclear. Here, we explored the role of B cells in evoked and spontaneous pain following neuropathic

injury through the production of autoantibodies. Adult male and female wild-type (WT) and B cell-deficient (muMT) mice received unilateral chronic constriction injury (CCI) of the sciatic nerve or sham surgery. Mechanical allodynia was assessed using von Frey filaments. WT mice developed mechanical allodynia within 7 days following CCI, while B cell-deficient mice were protected from developing allodynia. Spontaneous pain, which is often the chief complaint of those with neuropathic pain, was assessed using the conditioned place preference assay with a 50 mg/kg dose of gabapentin following 4 days of pairing. Both WT and B cell-deficient mice showed reinforcing effects of gabapentin, which may be due to the anxiolytic effects of the drug. Immunofluorescence microscopy revealed increased accumulation of immunoglobulin G (IgG) antibodies in ipsilateral L4-5 dorsal root ganglia (DRG) on day 21 following CCI. Intensity of brain lipid-binding protein (BLBP), a marker of satellite glial cells (SGCs), was also elevated in ipsilateral DRG at day 21 following CCI. These data suggest that IgG antibodies may bind to SGCs to release factors that contribute to neuronal hyperexcitability, which may influence mechanical allodynia following peripheral nerve injury.Funding: Cincinnati Children's Hospital Department of Anesthesia Innovation and Pilot Grant (MJL).

Aha1 Inhibition Enhances Morphine Analgesia In Post-operative Pain Model
Ishrat Jahan, Nisreen Manago, Samantha Romero, Brian SJ Blagg, Wei Lei; Purdue University Fort Wayne

Improving opioid therapeutic index (increased analgesic effect with reduced side effects) has been an approach for enhancing pain management. Our previous studies have demonstrated that spinal inhibition of heat shock protein 90 (Hsp90) can improve morphine analgesic effect without increasing the side effects through activating ERK-RSK signaling. However, universal Hsp90 inhibition causes severe side events, such as liver toxicity. Therefore, a more selective approach that targets the Hsp90 mechanism is desired for improving opioid therapy. Our preliminary data find that spinal inhibition of activator of Heat Shock Protein 90 ATPase (Aha1), a co-chaperone of Hsp90, enhances morphine anti-nociception in the tail-flick mouse model. In this study, we extend our investigation to the impact of KU-177, an Aha1 inhibitor, on morphine analgesia in post-operative pain and morphine side effects. We also evaluate the effect of KU-177 on the pain and opioid signaling pathways in brain and spinal cord. We have found that systemic intraperitoneal administration of KU-177 has no effect on liver weight. We also demonstrate that treatment with KU-177 significantly amplified morphine analgesic effect in the post-operative pain model, without changing the morphine withdrawal symptoms. We are investigating the molecular mechanisms by analyses of protein expression and activation in the spinal cord, brainstem, and periaqueductal gray (PAG). In summary, Aha1 inhibition could be an approach for improving therapeutic index, even the exact molecular mechanism remains unclear.

Adipocyte Adrb3 Drives Chronic Primary Pain By Increasing The Activity Of Nociceptors And Glial Cells
Yaomin Wang, Junli Zhao, Mona Hashemaghaie, Yufei Li, Marguerita Klein, Ru-Rong Ji, Andrea Nackley; Duke University School of Medicine

Chronic primary pain conditions (CPPCs) affect over 100 million people in US, predominantly women. Patients with CPPCs have genetic variants that lead to decreased activity of catechol-O-methyltransferase (COMT) and corresponding increases in basal and stress-induced levels of catecholamines in circulation. We established a novel mouse model of CPPCs that integrates clinically relevant COMT genetic vulnerability and stress to investigate underlying mechanisms. In prior work, we demonstrated that CPPC mice exhibit multi-site body pain, of greater magnitude and duration in females, and increased activity of primary afferent DRG nociceptors through activation of adrenergic receptor beta-3 (Adrb3). The purpose of the present study was to characterize the role of adipocyte Adrb3 in the development of pain and in regulating adipocyte-neuron interactions. We found that mice with conditional knockout of adipocyte Adrb3 failed to develop mechanical hypersensitivity at paw, abdominal, and back sites in the CPPC mouse model. Conditional knockout of adipocyte Adrb3 also reduced inflammation, characterized by decreases in DRG macrophages and neuroinflammation, characterized by decreases in spinal cord and the CA1 hippocampal microglia and astrocytes. Further, Adrb3-mediated antinociception is governed by suppressing excitability of nociceptors. Our findings reveal peripheral adipocyte-sensory neuron interactions as a critical regulator of nociception and identify adipocyte Adrb3 as a promising new target for treating CPPCs in the absence of central side-effects. NIH/NINDS R03 NS123731, R01 NS109541 and R61/R33 NS123753 to AN.

Dichotomous Action of Opioids on Striatal Projection Neurons Underlies Antinociception
Landon Bayless-Edwards, Haining Zhong, Tianyi Mao; Oregon Health & Science University

The dorsal striatum role in antinociception is thought to be mediated by opioids and opioid-induced dopamine release. However, the cellular signaling mechanisms underlying such function is not well understood. We hypothesized that protein kinase A (PKA), a mediator downstream of both opioid and dopamine receptors, may play a central role integrating these neuromodulatory signals intracellularly. Since MORs are Gi-coupled receptors, it predicts that opioids would reduce PKA activity. Distinct dopamine receptor expression on the two striatal projection neurons, dSPNs and iSPNs, predicts that dopamine would oppositely modulate PKA activity in each type of SPN. Thus, each cell type may differentially integrate these neuromodulatory signals, leading to unique downstream activity and effects on behavior. To examine longitudinal PKA activity with single cell resolution in vivo, we used two-photon fluorescence lifetime imaging of a novel PKA sensor in dSPNs and iSPNs. We found that PKA activity is tightly regulated by dopamine and opioids and underlies basal nociceptive threshold. Further, morphine causes opposing modulation of PKA in each SPN type, which underpins morphine-induced antinociception. This cell-type specific modulation of PKA activity is blocked by a MOR antagonist and the respective dopamine receptor antagonist. We confirmed that morphine induces dopamine release in the dorsal striatum with kinetics that align with PKA dynamics. In addition, we discovered that morphine-induced PKA dynamics modulate cell activity. Together, our results suggest that the integration of opioid and dopamine signals by PKA in both cell types is critical to maintain basal nociceptive threshold and morphine-induced antinociception. R01NS081071 (TM),F30DA057838 (LBE).

Exploration of Sub-Regions of The Insula Contributions to Sensory-gating of Noxious Stimuli Using Low-intensity Focused Ultrasound

Wynn Legon; Fralin Biomedical Research Institute

Several lines of evidence demonstrate increased activity of the insula to noxious and innocuous stimuli in chronic pain patients. Central sensitization (CS) may be the result of generalized CNS sensory amplification due to deficient central sensory gating mechanisms reflected as an increase in activity of the insula. As such, down-regulation of specific insular sub-regions may reduce hypersensitivity to noxious and innocuous stimuli. Here, we test if inhibition of different sub-regions of the insula (anterior and posterior) using low-intensity focused ultrasound (LIFU) affects sensory gating in healthy volunteers and patients with fibromyalgia (FM) and complex regional pain syndrome (CRPS). We employed a paired-pulse paradigm using contact heat to measure and test sensory gating in the insula. Two heat stimuli (6/10 pain rating) were delivered to the dorsum of the dominant hand with a 1 second interstimulus interval. Preliminary analysis demonstrates that FM and CRPS patients show a heightened response (N2/P2 vertex potential) to the second stimulus as compared to controls that show inhibition of this response. LIFU to the PI but not the AI served to increase gating in patient populations. LIFU to the insula had no effect in the healthy cohort. These data suggest that the posterior insula may be specific to pain gating and that LIFU may help to restore these mechanisms in patients with FM and/or CRPS.

Impact Of a Ketogenic Diet On Chemotherapy-Induced Peripheral Neuropathy

Lana L. Heslop, Trent Madden, Gentry Totta-Griese, Will Hauser, Sarah J. Crowards, Janelle Ryals, Heather M. Wilkins, Doug E. Wright; University of Kansas Medical Center

Chemotherapy-induced peripheral neuropathy (CIPN) is a condition in which peripheral nerves degenerate after exposure to neurotoxic chemotherapy agents. CIPN affects up to 68% of cancer patients, causing symptoms of pain, numbness, and tingling in the distal regions of the body. Bortezomib is one of the neurotoxic chemotherapies and induces CIPN in approximately 75% of patients. These CIPN symptoms can be so painful that chemotherapy treatments are reduced or stopped, and both options decrease patient survival rates. Therapeutic options for CIPN are limited, leading us to explore new avenues associated with dietary interventions. We conducted a ten-day study, administering intraperitoneal injections for five consecutive days of either vehicle or bortezomib (BTZ), followed by a five-day washout period in C57BL6 mice that received either a chow diet or a ketogenic diet throughout the entire study. Our results suggest that BTZ significantly reduced the intraepidermal nerve fiber density (IENFD) in mice fed a chow diet within five days, but mice given BTZ and fed a ketogenic diet were largely protected from IENFD reductions, suggesting that consumption of a ketogenic diet can prevent epidermal fiber loss in BTZ-induced CIPN. In addition, our results reveal that BTZ increased the extracellular acidification rate in dorsal root ganglion (DRG) neurons, while ketones increased the mitochondrial oxygen consumption rate. These differences in cellular metabolism suggest that BTZ and a ketogenic diet might be acting as opposing metabolic phenotypes. Ongoing studies include testing whether ketones can prevent BTZ-induced changes in neurite degeneration in

vitro. Funding: NIH R01NS043314-19 and 5P20GM103418.

Primary Afferent Neurons Do Not Contribute to Injury-Induced Latent Pain Sensitization
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Tissue injury leads to a very long-lasting latent pain sensitization (LS) in dorsal horn neurons that are kept in a state of remission by opposing Gi/o-protein coupled receptors, including μ-opioid receptor constitutive activity (MORCA). Whether activity at primary afferent neurons (PAN) is required for the development or maintenance of LS is unclear. To test this hypothesis, we initiated LS with either incision or CFA injection into plantar hindpaw, used multiple approaches to disrupt PANs, and then measured inverse agonist (naltrexone, NTX)-induced mechanical hypersensitivity and/or phosphorylated extracellular signal-regulated kinase (pERK, a marker of dorsal horn neuronal activity). Neither NTX-induced reinstatement of mechanical hypersensitivity nor stimulus-evoked pERK expression in dorsal horn were changed by various approaches to nerve block, including popliteal fossa injections of: 1) bupivacaine (5 mg/mL) at D21 following incision; 2) Exparel (an FDA-approved bupivacaine liposome injectable suspension) at D0-D12, D9-D21, and D21, following incision; or 3) lidocaine at D21 in both incision (1-20 mg/mL) and CFA models (2%; 100 μL) of LS. Multiple approaches to PAN ablation also failed to prevent or reverse NTX-induced reinstatement of hypersensitivity, including: 1) intrathecal administration of isolectin IB4-saporin (1.5 μg) to deplete non-peptidergic C fibers; 2) intrathecal capsaicin (50 mg/kg) to deplete peptidergic C fibers; or 3) conditional deletion of neurons expressing Mas-related G-protein coupled receptor member D (MrgprD+, a marker of IB4+ neurons) in a tamoxifen-inducible MrgprD-CreER mouse line. These data suggest that LS is driven by CNS mechanisms, independent of primary afferent drive.

Impact Of Maternal Care Behaviors On Mechanical Sensitivity Of Adult Offspring
Kayleigh Rodriguez, Laura Osborn, Dakota Redling, Mary Grace Bishop, Kimberly Stephens; University of Arkansas for Medical Sciences

Neuronal plasticity during the early postnatal period is sensitive to the duration and pattern of maternal care behaviors. Models of chronic early-life stress (CES) aim to disrupt maternal behavior by physical separation or depleted bedding and are associated with pain-related hypersensitivity in adult offspring. The impact of altered maternal behavior following resumption of standard conditions on mechanical sensitivity in adult offspring remains unknown. We subjected dams to limited bedding (CES) or standard (STD) cage conditions from postnatal day (PND)2-9. On PND10 litters returned to standard conditions. Half STD pups were fostered by a CES dam until weaning (STD/CES). The remaining dams continued to care for pups as assigned (STD, CES). Maternal behavior was recorded until weaning. At PND42, male and female offspring underwent Chronic Constriction Injury (CCI) and mechanical sensitivity assessed by von Frey. Assessors were blind to group assignment when possible. We found lower

baseline paw withdrawal thresholds (PWT) in CES compared to STD offspring (17.72±1.7 vs 24.45±1.8, $p<0.0001$). CES females had lower PWTs than CES males (16.58±1.5 vs 18.86±1.0, $p<0.01$). STD/CES offspring showed no difference from CES offspring, regardless of sex. Following CCI, CES males had lower PWT than STD males (5.8±0.7 vs 9.1±1.2, $p<0.01$) and females (2.0±0.4 vs 5.5±0.9, $p<0.001$). CES females had lower PWT than CES males (2.0±0.4 vs 5.8±0.7, $p<0.0001$). STD/CES offspring showed no differences in post-CCI PWT from CES animals. Dams exposed to impoverished environments maintain altered care behaviors upon return to standard housing that are sufficient to provoke mechanical hypersensitivity in adult offspring.

Neuronal p38 MAPK Signaling Contributes To Cisplatin-induced Peripheral Neuropathy
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Chemotherapy-induced neuropathy (CIPN) is a debilitating consequence of chemotherapy that may exist even after its discontinuation. We examined if p38 MAPK contributes to the progression of pain hypersensitivity in response to cisplatin treatment. We used a female transgenic mouse model showing the evolutionary spectrum of human breast cancer with a large T-antigen/C3 promoter (C3TAg) and wild-type FVB/N mice. We observed that cisplatin treatment of C3TAg and FVB/N mice stimulates p38 MAPK phosphorylation and nuclear translocation in DRG neurons, which is inhibited by cotreatment with neflamapimod, a selective p38α inhibitor. In vitro, cisplatin treatment of DRG neurons stimulated p38 MAPK phosphorylation and nuclear translocation, which was inhibited by neflamapimod, validating the in vivo observations. Neflamapimod inhibited cisplatin-induced oxidative stress, decreased mitochondrial membrane potential, and cleaved caspase 3 expression in primary DRG neurons from C3TAg mice. Neflamapimod also prevented cisplatin-induced axonal damage in DRG neurons, evinced by reduced sprouting of neurites from the soma and the maintenance of pseudo unipolarity in vitro. Functionally, neflamapimod significantly improved mechanical, musculoskeletal, and cold sensitivity in cisplatin-treated C3TAg and FVB/N mice. Our data suggests that targeting p38 MAPK with neflamapimod can potentially ameliorate the neuropathic consequences of chemotherapy. Neflamapimod is in clinical trials for neurodegenerative conditions and, therefore, has translation potential for treating CIPN in subjects with cancer.
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Effects of Early Life Stress on Postsurgical Pain Outcomes in Rats
Dakota Redling, Kayleigh Rodriguez, Mary Grace Bishop, Laura Osborn, Kimberly Stephens; University of Arkansas for Medical Sciences

Prolonged postsurgical pain increases healthcare utilization, postsurgical complications, and opioid usage. Adverse exposures in early life impact somatosensory development and have been

associated with increased neuronal excitability in primary sensory neurons and chronic pain later in life. However, little is known about how early life environment contributes to the trajectory of postoperative pain. In this study we used a well-established rat model of chronic early life stress (CES) to study how early life stress contributes to pain intensity and duration in adult offspring. Time-pregnant dams delivered without intervention. On postnatal day (PND) 2, the dam and her litter were transferred to a cage with standard bedding (STD group) or limited bedding (CES group) for PND2-9. On PND10 all animals were returned to cages standard bedding. Plantar incision was performed on CES (n=12) and STD (n=12) offspring on PND66. Mechanical sensitivity was assessed by von Frey at baseline (PND63) and each day following surgery until paw withdrawal thresholds (PWT) returned to baseline. Following plantar incision, PWT was lower in CES vs STD male (mean+SD, $p<0.01$) and female (mean+SD, $p<0.01$) offspring. CES offspring had a longer duration of hypersensitivity sensitivity than STD offspring (mean+SD vs mean+SD, $p<0.05$). Female CES offspring had a longer duration of postsurgical hypersensitivity than male CES offspring (mean+SD vs mean+SD, $p<0.05$). Our findings indicate that CES increased the intensity and duration of postsurgical pain in adult male and female rodents.

Truncated TrkB: Functional Insights In Nociceptors
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Brain-derived neurotrophic factor (BDNF) plays a pivotal role in various chronic pain conditions, including inflammatory, neuropathic, orofacial, and cancer-related pain. BDNF exerts its effects primarily by binding to its receptor, TrkB, initiating downstream signaling that modulates pain. TrkB exists in two splice variants: the full-length isoform (TrkBTK+), which signals through its kinase domain, and the truncated isoform (TrkBT1), which lacks the kinase domain but includes a unique 11-amino-acid sequence in its intracellular domain. While TrkBTK+ is well-characterized, our study identified TrkBT1 as the predominant TrkB isoform expressed in nociceptors and investigated its functional role. Using immunohistochemistry (IHC), western blotting, and single-cell RT-PCR, we characterized TrkB isoform expression in trigeminal ganglia. Calcium imaging was employed to assess calcium influx in sensory neurons following BDNF application and evaluate whether BDNF sensitizes capsaicin responses with or without the TrkB antagonist ANA12. Additionally, IHC was used to determine whether BDNF enhanced nociceptor survival in culture through TrkB-dependent mechanisms. Our results demonstrated that TrkBT1 is expressed in a broader population of sensory neurons, including nociceptors and non-nociceptors, compared to TrkBTK+. Further, BDNF increased calcium influx in sensory neurons, sensitized TRPV1+ nociceptors, and enhanced neuronal survival in culture—effects that were inhibited by ANA12 pre-treatment. These findings establish TrkBT1 as the predominant isoform in trigeminal nociceptors and highlight its functional role in BDNF-mediated nociceptor modulation. This work underscores the importance of TrkBT1 in pain biology and its potential as a therapeutic target.

Ly6e Glycoproteins as a Potential Modulators of NaV1.7 Channels and Drivers of Pain
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Ly6e Glycoproteins as Potential Modulators of NaV1.7 channels and Drivers of PainLy6e, a member of the Ly6 family of glycoproteins, can be secreted or membrane-anchored through a glycosylphosphatidylinositol (GPI) moiety. These proteins play crucial roles in cell adhesion and signal transduction within both immune and non-immune cells. Structurally, Ly6 proteins bear a resemblance to three-fingered snake venom toxins (3FTs), particularly α-neurotoxins, which are known to modulate ion channels. While the regulation of voltage-gated sodium channels by Ly6 proteins remains unexplored, studies on 3FTs provide compelling evidence suggesting their potential modulatory effects. For instance, the Naja atra venom peptide μ-EPTX-Na1a alleviates neuropathic pain by inhibiting NaV1.8 and altering its activation properties. Utilizing RNAScope, we observed an upregulation of Ly6e expression in the ipsilateral L3-L5 dorsal root ganglia (DRGs) neurons two weeks post-Spared Nerve Injury (SNI) compared to sham controls. Furthermore, we demonstrated that Ly6e interacts with NaV1.7 in mouse DRGs. Functional studies in HEK293 cells stably expressing NaV1.7 revealed that Ly6e overexpression increases NaV1.7 sodium currents. Similarly, overexpression of Ly6e in rat DRG neurons enhanced total sodium currents. Behavioral experiments demonstrated that intrathecal injection of Ly6e-pcDNA3 induced mechanical allodynia in naïve female rats within 24 hours. Finally, RNAScope analyses of human DRGs revealed Ly6e mRNA expression in both neuronal and non-neuronal cells. These findings collectively identify Ly6e as a potential regulator of NaV1.7 and suggest its involvement in pain regulation.

Exploring the Interplay of Empathy and Pain Perception in Romantic Relationships: An EEG Study

Sarah Love, Amber Harris Bozer; Tarleton State University

Exploring the Interplay of Empathy and Pain Perception in Romantic Relationships: An EEG StudySarah Love & Amber Harris Bozer Department of Neuroscience, Tarleton State University, Texas A&M System, Stephenville, TexasThe aim of this study was to investigate the potential relationship between empathy and mu rhythm suppression during observation of pain in romantic partners. The hypothesis was that empathy is correlated with greater mu suppression when participants are exposed to their partner in pain elicited by a cold pressor task. Heterosexual couples were recruited and administered the Toronto Empathy Questionnaire (TEQ), the Interpersonal Reactivity Index (IRI), and the McGill Pain Questionnaire. EEG activity was recorded in the electrodes of interest (C3, C4, Cz) at the following time points: (1) baseline with no pain and no consoling touch, (2) baseline with no pain and consoling touch, (3) in pain from a cold pressor task with no consoling touch, and (4) in pain from a cold pressor task with consoling touch. There was a negative correlation between activity in the Cz electrode and the TEQ data during the session with pain and no touch ($r=-.77$, $p=.043$). There were no other significant correlations. These data indicate that when participants observed a partner in pain and were not permitted to apply consoling touch, higher EEG activity was related to lower empathy scores. Interestingly, this relationship was not present when consoling touch was permitted. These

findings contribute to our knowledge about the role of the precentral motor cortex in empathy for pain.

Peripherally To Centrally Driven Neuroinflammatory Signaling In Paclitaxel-Induced Peripheral Neuropathy: Temporal, Sex, And Tissue-Specific Molecular Analysis
Yogesh Rakholia, Lauren Soleo, Priyam Das, Nolan A. Wages, M. Imad Damaj; Virginia Commonwealth University

Peripheral neuropathy is one of the most prevalent neurotoxic, dose-limiting side effects of paclitaxel, a chemotherapy agent used widely in solid cancers. The mechanism of paclitaxel-induced peripheral neuropathy (PIPN) is poorly understood, and thus there are no approved treatments currently. Notably, neuroinflammation has been described as a cardinal component in the pathogenesis of PIPN. However, animal studies of PIPN assessing neuroinflammation mediators have mostly focused on gene expression, not protein, and usually in one neuronal tissue and/or at one time point in male mice. Thus, a characterization of inflammation mediators in both sexes, in different neuronal tissues, and at different timepoints is critical to understanding PIPN. Paclitaxel (8 mg/kg, i.p.) or vehicle was administered every other day for a total of four injections in C57BL/6J mice. Mechanical and cold sensitivity, nerve conductance, and 22 cytokines and chemokines levels in the dorsal root ganglia (DRG) and spinal cord were measured at different time points (7, 14, and 21 days) in both sexes. Paclitaxel induced mechanical and cold hypersensitivity and decreased nerve conduction amplitude, the latter was more pronounced in male than female mice. Multiplex cytokine analysis revealed that paclitaxel induced increase in neuroinflammation is time-, sex-, and tissue- dependent. Our findings contribute to current knowledge about neuroinflammation as an important mechanism in PIPN and thus advance efforts to identify targets for novel therapies. In addition, the results inform us about potential mechanistic sex differences that can guide precision medicine.

Role of CD38 in Clonidine-Mediated Spinal Antinociception
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Understanding the mechanism of action of spinal analgesics can lead to the development of novel pain therapies. Both morphine and clonidine signal via inhibitory G-protein-coupled receptors (Gαi) in the spinal cord to produce antinociception. Our lab has identified CD38, a multifunctional enzyme primarily expressed in spinal astrocytes that converts NAD into cADPR and regulates intracellular calcium responses in an agonist-specific manner in other systems, as crucial for spinal opioid analgesia. Using CD38 knockout (CD38KO) and wild-type (WT) mice, this study examined the role of CD38 in the spinal thermal (TWL) and mechanical (MWT) antinociceptive effects of clonidine in non-injured and CFA-induced inflammatory pain models across sexes. The TWL and MWT of intrathecal (i.t.) administration of clonidine (10 nmol) were enhanced in CD38KO females but not in CD38KO males, compared to respective WT controls in both the non-injured and the CFA-induced inflammatory pain. Spinal NAD levels in non-

injured CD38KO were markedly higher than in WT mice, particularly in males. CFA treatment increased spinal NAD levels in CD38KO mice, particularly in females, and in WT males, while it decreased NAD levels in WT females. These findings suggest a potential female-specific negative spinal antinociceptive interaction between clonidine and astrocytic CD38. Further elucidation of the mechanisms underlying this interaction could help better understand sex differences in spinal antinociceptive mechanisms, and facilitate the development of novel therapeutic strategies.

Exploring the Role of Brain Extracellular Matrix in Chronic Pain: Neuron-Glia Crosstalk
Chuang Ge, Vaneeza Kausar, Areej Niaz, Lele Xu, Jacob Zirkiyev, Sebastian Alvarado, Rinat Abzalimov, Ye He, Maral Tajerian; City University of New York

Chronic pain affects 30% of adults in the United States and is associated with suffering, high costs, and lost productivity. Despite its prevalence, the mechanisms of pain chronification remain unclear. The brain extracellular matrix (ECM) plays a critical role in physiological and pathological conditions, particularly in its interactions with neuronal and glial cells. ECM components such as hyaluronic acid, chondroitin sulfates, proteoglycans, and glycoproteins are implicated in neuronal and glial plasticity. Our hypothesis is that maladaptive ECM remodeling disrupts neuron-glia crosstalk, contributing to chronic pain progression. Using a tibial fracture mouse model, we investigated ECM alterations and their impact on glial activity. Behavioral testing included tactile sensitivity, motor function, and memory assessments at baseline, acute (4 weeks), and chronic (7 weeks) phases. ECM changes were analyzed through imaging mass spectrometry and single-cell western assays. Preliminary results revealed decreased mechanical thresholds and memory deficits in injured mice, along with spatially distinct ECM protein changes. Prior research supports increased glial engulfment of neuronal dendrites in pathological states, and ongoing studies aim to elucidate the specific mechanisms of ECM-induced neuronal reorganization. These findings underscore the importance of ECM in chronic pain, offering potential therapeutic targets to mitigate maladaptive neuron-glia interactions.

Dissociating The Neural Circuitry Underlying The Modulation Of Distinct Nociceptive Behaviors
Isabel Bleimeister, Suhjin Lee, Sarah Ross; Pittsburgh Center for Pain Research

Stimulation of the ventral lateral periaqueductal grey (vlPAG) is known to be anti-nociceptive (Reynolds, 1969; Mayer et al., 1971). A circuit involving vlPAG projections to the rostral ventral medulla (RVM) has been previously implicated in promoting descending inhibition of nociceptive input at the level of the spinal cord (Behbehani & Fields, 1979; Fields & Heinricher, 1985). However, though activation of this projection has been found to increase withdrawal latencies in assays measuring spinally mediated reflexes, the role of this pathway in modulating more complex pain behaviors is unknown. To evaluate the role of descending inhibition from the vlPAG in non-reflexive pain behaviors, efferent projections from the vlPAG to other supraspinal structures were assessed anatomically and behaviorally through the use of viral tracing and

chemogenetics. Withdrawal latencies and affective measures were assessed across a variety of nociceptive assays and distinct nociceptive behaviors were found to be modulated by dissociable projections from the vlPAG. Specifically, though activation of the vlPAG to RVM pathway did inhibit select noxiously evoked spinal reflexes, activation of this pathway failed to recapitulate all of the complex behaviors evoked by gross vlPAG stimulation in the context of pain suggesting that the projection from the vlPAG to the RVM is not the sole pathway underlying vlPAG stimulation-induced anti-nociception but rather, it is one of several vlPAG output pathways involved in the modulation of pain behaviors. Funding: F31NS134315.

Temporal Characterization of Radiation-Induced Oral Pain Using A Mouse Model
Ashlyn G. Rickard, Megan A. Atherton, Joseph O. Veliz, Lisa A. McIlvried, Yvonne M. Mowery, Nicole Scheff; University of Pittsburgh

Pain during radiation therapy (RT) for head and neck cancer (HNC) is a major clinical challenge with variable management. Radiation-induced pain typically co-develops with oral mucositis (OM), an inflammatory condition in the mucosa that affects function and ability to tolerate treatment. Preclinical efforts are needed identifying new therapeutic options; however, standardized RT-induced pain models are lacking. We developed a novel, mucostits-pain mouse model,induced by focal, image-guided RT that uses both single and multi-fractionated regimens. Adult naïve C57Bl/6 mice and a syngeneic orthotopic HNC mouse model were used to characterize RT-evoked nociceptive behavior, changes in body condition, OM development, and sensory nerve injury and regeneration responses. Naïve mice that received single fraction RT (15Gy) or multifractionated dosing (8Gyx3 fractions) localized to the anterior oral cavity experienced peak weight loss (-26±5% loss from baseline) at post-RT day (PRD) 10. However, hypersalivation and tongue ulcerations were identifiable as early as PRD 8. Mice demonstrated a 46.1±20.7% increase in grimacing behavior at PRD 9, as measured by PainFace grimace assay. Additionally, we found a 3-fold increase in ATF3 expression in mandibular trigeminal neurons on PRD 10 compared to sham RT. Lastly, using a syngeneic buccal tumor model, we observed a substantial increase in tumor tissue nerve innervation using S100-immunoreactivity 10 days after focal RT compared to sham-treatment, suggesting that RT can induce neuronal sprouting in the oral cavity. These data begin to fill an important gap in knowledge in the cancer pain field, allowing for development of new strategies to treat radiation-associated pain.

Single-dose, Non-Opioid Nanomedicine Analgesic for Battlefield Pain Control with Neuromuscular Regenerative Effects
Jelena Janjic, John Pollock, Vijay Gorantla; Duquesne University School of Pharmacy

The Army Regional Anesthesia and Pain Management Initiative identified the critical need for effective pain management in the acute phase, during military treatment facility care, and during rehabilitation and recovery. There is a need for a single-dose, long-acting analgesic without cardiovascular or respiratory effects, performance-limiting effects (e.g., sedation), or interference with other treatments and interventions that can be quickly administered on the battlefield by a

medic to provide effective pain control. We present an innovative Non-Opioid Nanomedicine Analgesic platform with a single-dose, parenteral administration that achieves injury-specific, targeted immunomodulation, produces analgesia, and promotes neuromuscular regeneration. Rodent and non-human primate results are presented. We found that the nanomedicine promoted axon survival and myelin preservation following sciatic nerve transection and repair in a rat, while the untreated controls were associated with extensive myelin disruption and axonal loss. In Cynomolgus macaques (n=3 per group), we tested the nanomedicine as a single-dose analgesic against the standard of care. Radial nerve transection and repair surgery was used as a nerve injury model, followed by wrist-extension behavior, electrophysiology, and near-infrared fluorescence imaging inflammation assessments, along with clinical evaluations. The animals that received a single i.v. dose of nanomedicine at the point of surgery showed marked improvement in behavior, reduced inflammation, accelerated surgical wound healing, and improved nerve sensory conduction compared to the standard of care (i.m. meloxicam daily). Our preliminary results demonstrate the utility of pain nanomedicine as the future single-dose analgesic for battlefield and other trauma-induced pain. Funding: CDMRP Award W81XWH-20-1-0276.

Microglia Mediated Neuroinflammation Contributes To Hyperalgesia In A Rodent Model Of Chronic, Widespread Pain

Anna Ramirez, Luiz Ferrari, Norman Taylor; University of Utah

We recently identified the Dahl salt-sensitive (SS) rat as a rodent model of inherited, widespread hyperalgesia. SS rats show several additional phenotypes consistent with nociplastic pain conditions, such as dysfunction in descending pain modulation and stress response systems, along with increased sensitivity to hyperalgesic mediators and fatigue-like behaviors. These characteristics make the SS rat a model system to study mechanisms of nociplastic pain. We previously administered dexamethasone and indomethacin to male SS rats and found both drugs only had modest effects that did not reach clinical significance (Ferrari 2022). To determine if there was evidence of neuroinflammation in SS rats, microglia reactivity was evaluated by immunohistochemical Iba1 staining in the periaqueductal gray (PAG) of adult male SS compared against Sprague Dawley (SD) rats. Microglia morphology was then evaluated using the MATLAB based script 3Dmorph. Then to determine the significance of this neuroinflammation on hyperalgesia, the non-specific microglial inhibitor minocycline was administered daily for 5 days (30 mg/kg, i.p.) and the Randall-Selitto method was used to evaluate nociceptive thresholds 24 hours after each injection. We found that male rats showed increased area of Iba1 staining and more ameboid morphology compared with control SD rats. In addition, both male and female animals showed a significant increase in nociceptive threshold after treatment with minocycline (male: from 75.33 g to 100.0 g $p<0.0001$, female: 65.42 g to 79.31 g, $p=.0009$). Taken together these findings indicate that microglia reactivity plays an important role in SS rat hyperalgesia.

Analgesic-Induced Organ Damage In Sickle Mice: Protective Role of Heme Oxygenase-1 And Cyp3a11.

Ashley Smith, Nandhine Rajasekhar, Tomasz Kaminski, Prithu Sundd, Tirthadipa Pradhan-Sundd; Versiti Blood Research Institute

Pain and organ damage are major comorbidities of sickle cell disease (SCD). Individuals with SCD are often on analgesics for pain management which are metabolized by the liver and excreted through the kidneys. However, the long-term effect of these drugs in the liver and kidney of SCD remains under examined. Using real time intravital imaging of live SCD mouse we analyzed the effect of acetaminophen on the liver of humanized transgenic Townes HbSS sickle and littermate control mice under acute and chronic treatment. We found opposite effects in the liver of sickle mice after acute and chronic treatment with acetaminophen. Sickle mice were able to better tolerate acetaminophen treatment acutely, but in the long run ickle mice post acetaminophen treatment showed delayed resolution of liver injury and exacerbated fibrosis compared to control mice. Mechanistically we observed that sickle mice were protected from cytotoxicity caused by acetaminophen at baseline due to significant activation of hepatic Kupffer cells which produced heme-oxygenase 1 (HO-1). HO-1 promoted the activation of cytoprotective enzyme Cyp3a11 which accelerated hepatic degradation of a wide variety of lipophilic drugs including analgesics in a NRF2 independent manner. However, depletion of hepatic Kupffer cells upon acetaminophen treatment led to a reduced expression of HO-1 which inhibited the activation of Cyp3a11 in the liver exacerbating fibrosis and delaying resolution of liver injury and inflammation. Our mechanism-based preclinical data provide the first proof-of-concept of HO-1 and cyp3a11 as treatable targets for analgesic induced liver damage in SCD.

Understanding the Contributions of Kappa Opioid Receptors in Regulating Dopamine and Pain after Adolescent Ethanol Exposure: Sex-Dependent Neurobiological Changes

Abigail Kelley, Madison Heitkamp, Anushree Karkhanis; Binghamton University

Alcohol consumption in adolescence promotes pain hypersensitivity. In rats, adolescent chronic intermittent ethanol (aCIE) exposure facilitates dopamine release in the NAc shell with an associated augmentation in pain sensitivity, an effect reversed by chemogenetic inhibition of dopamine. Like dopamine, kappa opioid receptors (KORs) are involved in regulating alcohol use and pain sensitivity. Here we examine the effect of aCIE exposure on the KOR-dopamine interaction in the NAc shell and the associated impact on pain sensitivity during protracted abstinence. Male and female Long-Evans rats were exposed to air or ethanol vapor from PD28-65. Von Frey filaments were used to assess tactile sensitivity and accumbal dopamine kinetics were measured using ex vivo fast-scan cyclic voltammetry during protracted abstinence. Global activation of KORs with U50,488 attenuated tactile sensitivity in male and female aCIE-exposed rats at both the low (1.25 mg/kg) and high (2.5 mg/kg) doses, while only the high dose was effective in air-exposed controls, indicating a hyperresponsivity of KORs in aCIE-exposed animals. In the NAc shell, the impact of aCIE exposure on KOR-mediated inhibition of dopamine was sex-specific, such that, aCIE exacerbated KOR-mediated dopamine inhibition selectively in females. Interestingly, acute ethanol treatment-associated potentiation in KOR-mediated dopamine inhibition was dampened in aCIE- compared to air-exposed female rats. Ultimately, aCIE exposure-associated augmentation in tactile sensitivity was mitigated by KOR activation at higher potency. At least in females, this effect may be driven by a KOR-dependent

mechanism that controls dopamine. These sexually dimorphic data highlight the importance of developing sex-specific pain management treatment options.

QX-314: Lidocaine Derivative As a Candidate For Selective Targeting Of Nociceptive Fibers

Krista Mercado, Steve Davidson; University of Cincinnati College of Medicine

QX-314 is a quaternary lidocaine derivative that cannot directly penetrate the cell membrane, but has been shown to permeate activated TRPV1 and TRPA1 channels. Both channels are found in nociceptors, which should essentially give QX-314 selectivity for activated pain fibers. In this study, we aim to determine: (1) Whether QX-314 can directly activate nociceptors from mouse and human dorsal root ganglia in the absence of a TRP channel agonist; and (2) Whether co-administration of QX-314 with chloroquine—thought to indirectly activate TRPA1 channels—leads to a reduction in cell activation. Primary mDRG and hDRG cultures were created and neural activation was analyzed using ratiometric calcium imaging. The cells were exposed to QX-314, and the percentage of cells that responded was recorded. 11.2% of the mDRG cells responded directly to QX-314, while only 2.0% of hDRG cells responded. This suggests that QX-314 can directly activate both mDRG and hDRG cells, but not potently enough to rule it out as a candidate for selective pain inhibition. In a subsequent set of experiments, either chloroquine + QX-314 or chloroquine alone was administered to mDRG, and the magnitude of the following response to KCl was measured. The average response after application of chloroquine + QX-314 showed a 7.9% increase over baseline, compared to a 10.1% increase over baseline for the control group which received chloroquine alone. Co-administration of QX-314 with chloroquine led to a statistically significant suppression of nociceptor activation, which suggests that QX-314 could potentially be used to inhibit pain signals. NIH: R21AR068012.

Sex-specific Changes in Monoamine Transmission During Acute Inflammatory Pain and Across Recovery

*Madison Heitkamp, Alston Zhuo, Zoe Silverman, Anushree Karkhanis;*Binghamton University

Pain and mood disorders are often comorbid. Recent literature identifies pain-associated functional changes in the nucleus accumbens (NAc) shell. Dopamine and serotonin within the NAc shell, regulate mood and may be especially vulnerable to pain induced adaptations. However, current literature does not identify these alterations. Thus, we measured accumbal dopamine and serotonin response to acute and persistent pain in male and female Long-Evans rats using in vivo fiber photometry. We infused a genetically modified dopamine (pAAV-hSyn-dLight1.1) or serotonin (pAAV-hSyn-GRAB_g5-HT3.0) sensor and placed fiber optic probes into the NAc shell. Following virus incubation, we measured paw withdrawal threshold using Von Frey fibers and the associated changes in accumbal dopamine or serotonin before (baseline) and 2-, 7-, and 14-days after induction of inflammatory pain by administering Complete Freund's Adjuvant (CFA; 40 uL, intraplantar). At baseline, female rats exhibited greater paw sensitivity compared to male rats; however, following CFA administration, both sexes displayed comparable

pain potentiation. Males and females recovered to their baseline differences in paw sensitivity 14 days post-CFA. While females exhibited a pain-associated augmentation in dopamine levels, which recovered as typical tactile sensitivity recovered, accumbal dopamine did not change in males. In both sexes, serotonin activity decreased as pain sensitivity increased, recovering over time. Overall, these data indicate that pain potentiates opposing dopamine and serotonin activity in the NAc shell in females while only reducing serotonin in males. Thus, pain may disrupt the typical modulatory balance between dopamine and serotonin, which could augment pain perception and affective dysregulation.

Therapeutic Effect of Epidural Dexamethasone Palmitate in a Rat Model of Lumbar Spinal Stenosis

Joon -Hee Lee; Seoul National University Bundang Hospital

Therapeutic effect of epidural dexamethasone palmitate in a rat model of Lumbar spinal stenosisBackground: This study proposes Dexamethasone Palmitate(DEP) as an original therapeutic option for epidural injection, aiming to provide safer, more effective, and enduring pain relief for foraminal stenosis . Methods: Forty rats were randomly divided into four groups: epidural administration of sodium chloride solution (n = 10); DEX (n = 10); DEP (n = 10); and sham (n = 10). A single injection of DEP (0.8 mg/kg), DEX (0.5 mg/kg), or NS (250 μl) was administered. Mechanical stimulation and motor dysfunction were monitored for up to 21 days. Hematology and blood chemistry analyses were conducted one week after drug therapy. Tissue was collected to assess the degree of adhesion, inflammation in the perineural area, chromatolysis in the dorsal root ganglion, and adrenal gland for steroid pathology examination.Results:The DEX and DEP groups demonstrated significant recovery from mechanical allodynia and motor dysfunction after two weeks of drug therapy ($P < 0.001$). However, by the third week, the effect of DEP persisted compared to that of DEX diminished. Furthermore, the Dep group exhibited reduced fibrosis and less chromatolysis compared to the NS group. Conclusion:These results suggest that DEP shows potential as a treatment option for lumbar spinal stenosis-related pain, offering prolonged pain relief with fewer adverse effects compared to conventional approaches.

Functional Classification of Primary Sensory Neurons Using Two-Photon Calcium Imaging

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Primary sensory neurons are highly diverse and are tuned to detect a wide range of sensory inputs including tactile, thermal, and chemical stimuli. Noxious input is detected by a specialized class of sensory neurons, called nociceptors, that detect high threshold stimuli to avoid potential tissue damage. Identifying sensory neurons associated with the detection of specific stimuli could allow targeting of these neurons to silence their function in pathological states, such as in cases of neuromodulation for chronic pain. The diversity of sensory neuron types has made specific targeting problematic. Recent efforts to separate sensory neurons into subgroups have

largely focused on the genetic identity of these neurons, which do not consider their functional properties. To identify functionally distinct populations of primary afferent neurons, we use two-photon calcium imaging in our ex vivo somatosensory preparation where the skin of the hindlimb, peripheral nerves, DRG, dorsal roots, and spinal cord are dissected in continuum. Using this preparation, we performed natural stimulation of the skin to separate neurons based on their responses to tactile stimulation, heating, and cooling. We combined this unique approach with pharmacology, electrical threshold determination, and genetic identification using recombination to yield a multifaceted perspective on a neuron's functional identity. Collectively, these studies revealed that distinct classes of large diameter primary afferent neurons were activated following DRG stimulation, which suggests these neurons underlie the efficacy of DRG stimulation for the treatment of chronic pain. Supported by T32NS073548 to HJS, R01AR063772, R01NS096705 to SER and HRK, and RM1NS128775 to HRK.

Peripheral Opioid Receptor Signaling Masks cAMP-Induced Nociceptive Hypersensitivity Through KATP Channel Activation

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In a broad range of inflammatory pain models, cyclic AMP produced by adenylyl cyclases downstream of Gs-coupled receptors contributes to nociceptor sensitization. We used local injection of the adenylyl cyclase activator forskolin (FSK) to directly induce cAMP production in vivo. Hindpaw FSK injection in mice induced transient heat hypersensitivity compared to vehicle controls that resolved within 4 hours. However, 3 days after FSK injection, systemic injection of the peripherally-restricted mu opioid receptor antagonist naloxone-methiodide reinstated heat hypersensitivity in FSK-treated mice, but not in vehicle-treated mice. These results suggest that FSK-induced nociceptor sensitization had not resolved after 72 hours, but that it was masked by peripheral opioid antinociceptive signaling. Several reports indicate that peripheral opioid analgesia is mediated through activation of ATP-sensitive K+ (KATP) channels. Therefore, we injected another cohort of mice with FSK or vehicle and measured noxious heat thresholds at 1 and 72 hours to demonstrate initiation and resolution of hypersensitivity. After resolution of hypersensitivity, mice received a hindpaw injection of the KATP channel inhibitor glibenclamide, and noxious heat thresholds were measured 30, 90 and 180 min after injection. Glibenclamide injection reinstated heat hypersensitivity at 30 and 90 minutes in FSK but not in vehicle-treated mice. Hypersensitivity resolved by 180 min post-glibenclamide. Together, these results suggest that sustained activation of KATP channels by peripheral opioid signaling leads to the resolution of behavioral heat hypersensitivity by suppressing excitability in nociceptors that are persistently sensitized to heat. This phenomenon may cause enhanced vulnerability to subsequent injury.Funding: R01NS109936.

Schwann Cell Glial Cell Line-Derived Neurotrophic Factor Signaling Influences Pain In Neurofibromatosis 1

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Neurofibromatosis 1 (NF1) is a genetic disorder, characterized by a predisposition to benign tumor development with clinical manifestations like, cutaneous and plexiform neurofibromas, café au lait spots, and cognitive dysfunction. Pain, however, remains one of the most debilitating features interfering with routine activities in patients with NF1. Recent work from our lab has suggested that glial cell line-derived neurotrophic factor (GDNF) may be released from Schwann cells (SC) and may play an important role in the onset of pain due to NF1. The current study aims to determine if SC derived GDNF binds to its receptor GDNF family receptor-α1 (GFRα1) on neurons to regulate nociception in a preclinical model of NF1.Our results show that behavioral assessment of mice with SC specific deletion of Nf1 (DhhCre;Nf1fl/fl) that were injected with an AAV9 containing a shRNA against GFRα1 into the sciatic nerves, displayed significantly reduced mechanical hypersensitivity normally observed at 4-5 months of age in this mouse model of NF1. This correlated with the desensitization of myelinated A-fiber nociceptors and unmyelinated polymodal C-fibers (CPM) to mechanical stimuli compared to controls as assessed using a novel ex vivo hairy skin/saphenous nerve/DRG/spinal cord/ recording preparation. Together this indicates that GDNF-GFRα1 signaling from SC to neurons is a major contributor to pain in this tumor predisposition syndrome and targeting this pathway may be a novel cell-specific treatment strategy to ameliorate pain in NF1 patients.

Compartmentalized Signaling Of Mas-related G-protein Coupled Receptor X1 (MrGPRX1) And Transient Receptor Potential Vanilloid (TRPV) Channels In Pain And Itch Pathways

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G protein-coupled receptors (GPCRs) and TRPV (transient receptor potential vanilloid) channels are crucial for signal transduction in various physiological processes, including neurotransmission, pain perception, and itch. Downstream effectors of GPCR signaling can either directly stimulate TRPV channels or enhance their sensitivity to activating stimuli, a process known as TRPV sensitization. Traditionally, GPCRs are activated at the cell surface by extracellular agonists, triggering signaling cascades. Recent evidence suggests compartmentalized signaling of GPCRs from intracellular organelles. The human Mas-related G-protein coupled receptor X1 (MrGPRX1) is a GPCR expressed in primary sensory neurons involved in nociception and pruritus. However, there is no evidence that MrGPRX1 can signal from intracellular compartments. In this study, we characterized MrGPRX1 signaling within the endosomal network and its role in sensitizing TRPV channels to enhance pain and itch signaling. Utilizing recently developed cellular biosensors, we demonstrated MrGPRX1's ability to traffic and signal from endosomes. Immunofluorescence analysis showed that MrGPRX1 internalizes following BAM8-22 stimulation. BRET assays revealed that MrGPRX1 activation induces Gaq and B-arrestin-1 protein recruitment to the plasma membrane and early endosomes. Pharmacological and genetic inhibition of dynamin or clathrin blocked BAM8-22-induced MrGPRX1 endocytosis and decreased activation of nuclear extracellular signal-regulated kinase. Additionally, calcium imaging assays confirmed that MrGPRX1-mediated TRPV sensitization is

protein kinase C dependent. Our findings reveal a novel role for MrGPRX1 endosomal signaling in TRPV sensitization. Understanding the mechanisms of MrGPRX1 signaling offers valuable insights into differentiating between pain and itch pathways, aiding in the development of targeted therapies for chronic pain and persistent itch.

BAM! Investigating the Role Of Meningeal Macrophages and Receptor Activity-Modifying Protein 1 in Migraine Behavior and Etiology

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Migraine, a headache disorder characterized by throbbing head pain, nausea, and light/ sound sensitivity, affects about 1 billion people worldwide . It is suggested sensitization of trigeminal ganglion neurons that innervate the meninges, a release of calcitonin gene-related peptide (CGRP), and inflammation of the meninges are involved. Yet, the specific mechanisms and cell types through which CGRP and its receptor, Receptor Activity-Modifying Protein 1 (RAMP1), contribute to the cause of migraines are not fully understood. Recent studies highlight the importance of RAMP1-CGRP signaling of macrophages to elicit a pain response (Fattori, 2024). The purpose of our study was to investigate the role of macrophages in the context of migraine. Moreover, our cytokine array analysis showed a significant increase in the CX3CL1, a ligand that can activate macrophages, in mice of both sexes. We employed a well-established restraint stress-induced headache mouse model and found that stress induced facial allodynia, measured by von Frey, and higher meningeal CGRP release compared to controls. Preliminary flow cytometry data also suggests that RAMP1+ meningeal immune cells are disproportionately border associated macrophages (BAMs). BAM deletion (Pf4-DTR) prevented stress-induced facial allodynia. This data together suggests that meningeal macrophages play a vital role in migraine behavior and etiology. As a result, we have generated a Pf4-RAMP1 mouse line to further investigate the role of RAMP1 signaling on macrophages in migraine.

Sex-Specific and Neuronal Subtype-Specific Changes in Gene Expression in the Prefrontal Cortex in a Mouse Model of Neuropathic Pain

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Neuroplastic changes in the prefrontal cortex (PFC) are associated with chronic pain, yet the neuronal subtypes driving these changes are unclear. The aim of this study is to identify neuronal subtype- and sex-specific changes in gene expression in the PFC following nerve injury, utilizing single-nuclei RNA sequencing.Spared nerve injury (SNI) or sham surgery control were performed on 10-12 week-old C57BL/6 male and female mice to model neuropathic pain. Mechanical and cold sensitivity were assessed in the ipsilateral hind paws using the von Frey and acetone tests. PFC tissue was collected, snRNA-seq was performed using the PARSE platform, and data were analyzed using Seurat (v5) and pathway analysis (clusterProfiler).SNI resulted in hypersensitivity to mechanical and cold stimuli. Excitatory (Slc17a7+) and inhibitory (Gad1+, Gad2+) neuronal populations were identified and classified based on layer-specific and cluster-specific gene expression profiles. Notably, nerve injury induced upregulation of Fos and Myd88

in both excitatory and inhibitory neurons of male mice. Hundreds of differentially expressed genes (adj. $p < 0.05$) were identified in excitatory and inhibitory neurons, with distinct patterns between sexes. GO Pathway analysis revealed significant enrichment in processes including nervous system development, synapse organization, cellular component organization, and cell projection organization, with differences observed between neuronal subtypes and sexes.These findings suggest that sex-specific, neuronal subtype-specific changes in gene expression within the PFC could contribute to the onset and persistence of chronic pain. The identification of these genes and pathways may offer new potential targets for therapeutic interventions in a sex-specific manner.

Targeting Epidermal Langerhans Cells in Painful Diabetic Neuropathy: Bridging Mouse and Human Data

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Painful Diabetic Neuropathy (PDN), one of the most common and intractable complications of diabetes, is characterized by the remodeling of cutaneous innervation and neuropathic pain. Emerging evidence suggests a pivotal role of epidermal resident immune cells, such as Langerhans cells (LC), in maintaining neuropathic pain in PDN. Using the high-fat diet (HFD, 42%fat) mouse model of PDN, we show that increased LC density in the paw epidermis of HFD-fed male mice correlates with mechanical allodynia. LC ablation through a diphtheria toxin-mediated strategy effectively prevents mechanical allodynia and spontaneous pain, indicating the essential role of these cells in HFD-induced neuropathic pain. Transcriptional analysis of epidermal LC revealed molecular pathways involved in the neuro-immune communication between LC and nociceptive terminal afferents.Additionally, through a comprehensive cytokine profiling assay, we identified a panel of inflammatory molecules secreted by LC and potentially linked to PDN.Notably, we observed increased secretion of Mcp-1/Ccl2 by HFD LC. To enhance the translational relevance of our findings, we validated our results using human skin biopsies from PDN patients and controls. Our analysis revealed that a higher LC number in the epidermis correlates with small-fiber neuropathy in PDN patients. Further, to delineate the transcriptional signature of LC in PDN, we performed single-nuclei transcriptomics of human skin tissues, identifying novel genes in LC that could serve as potential therapeutic targets. Our research establishes LC as contributors to PDN through neuro-immune interactions and inflammation. By bridging animal and human data, we propose that LC represent promising targets for novel topical treatments for PDN. Fundings: R01 NS104295-01; HEAL INTIATIVE S3 R01 NS104295-01; AR077691-01.

Targeting STAT3 Signaling to Promote Recovery from Neuropathic Pain

Andrew Shepherd, Caitlyn Gaffney, Angela Casaril, Kristina Grove, Steve Schapiro, Moses Kasembeli, Cobi Heijnen, David Tweardy; The University of Texas MD Anderson Cancer Center

Targeting STAT3 Signaling to Promote Recovery from Neuropathic PainCaitlyn Gaffney1, Angela Casaril1, Kristina Grove2, Moses Kasembeli3, Steven Schapiro2, Cobi Heijnen4, Andrew Shepherd1, David Tweardy31The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USANerve injuries result in an increase of inflammatory mediators being released to the site of injury activating STAT3 signaling. This activation increases inflammation, oxidative stress, and impaired barrier function in the injured nerve. We hypothesize that STAT3 signaling in macrophages is a key pathway leading to neuropathic pain following nerve injury. We have developed a small-molecule STAT3 inhibitor, TTI-101, that is currently in clinical development. We aimed to determine if inhibition of STAT3 by TTI-101 reduces neuropathic pain caused by spared nerve injury (SNI) and chronic constriction injury (CCI) and promotes lasting functional recovery in mice by suppressing inflammation. We show, the administration of TTI-101 for 5 consecutive days promotes the recovery of neuropathic pain induced by SNI and CCI for up to 56 days. Specifically, TTI-101 reverses SNI and CCI-induced mechanical hypersensitivity. However, we do not see major gait changes between TTI-101 and vehicle treated mice. Considering that CD68 is a pan-macrophage marker, instead of reducing the population number, TTI-101 may be shifting the macrophage phenotype from a pro-inflammatory to an anti-inflammatory pro-resolution state, contributing to nerve regeneration to promote a long-lasting recovery. Further studies are needed to assess the effect of TTI-101 on inflammatory mediator production, oxidative stress, and nerve barrier function in mice subjected to SNI and CCI.

Inflammatory Neuropathy in Mouse Models of Colorectal Cancer: Implications for Chemotherapy-Induced Peripheral Neuropathy

Angela Casaril, Caitlyn Gaffney, Iqbal Mahmud, Bo Wei, Lei Shi, Theresa Guise, Phillip Lorenzi, Carolyn Hodo, Andrew Shepherd; The University of Texas MD Anderson Cancer Center

Colorectal cancer (CRC) is the second most common cause of cancer death in the US. Various treatment regimens have improved survivorship; however, these oxaliplatin-based regimens, including 5-fluorouracil, leucovorin and oxaliplatin (‘FOLFOX’), cause prolonged neurological symptoms in up to 80% of patients. Preclinical studies of chemotherapy-induced peripheral neuropathy (CIPN) have historically tended to use young-adult, cancer-free, male rodents that are naïve to surgery. Here, we developed a combined model of orthotopic colorectal cancer and adjuvant oxaliplatin, to more accurately replicate clinical CIPN. We first show neuronal dysfunction directly induced by tumor growth alone. Mice with CRC develop peripheral neuropathy associated with subtle locomotor deficits, without overt hypersensitivity. Peripheral nerves from CRC mice show widespread differences in pro-inflammatory cytokines and lipid metabolites, along with macrophage accumulation and myelin decompaction. In DRG neurons, ryanodine receptor oxidation was associated with dysfunctional Ca2+ homeostasis and reduced spike amplitude. These findings suggest CRC can be causally linked to a subacute form of chronic inflammatory demyelinating polyneuropathy. Indeed, matched dosing of oxaliplatin or a FOLFOX-like regimen caused more persistent hypersensitivity in CRC mice. Collectively our data suggest that subclinical neuropathy secondary to CRC may represent an under-reported, yet important risk factor for persistent neurological dysfunction in CRC survivors.

Acute Effects of Antibiotics on Nocifensive Behaviors and Dorsal Root Ganglia Neuronal Activity

Ashley Plumb, Jane Brandon, Joseph Lesnak, Theodore Price, Katelyn Sadler; University of Texas at Dallas

Abdominal pain is a common side effect of antibiotics, but the mechanisms underlying this symptom are unclear. Previous studies in mice have reported visceral and somatic pain after ingestion of various antibiotic drugs, though often at clinically irrelevant doses. It remains unknown if or how different classes of antibiotics administered at clinically relevant doses induces pain in rodents. To explore this question, C57BL/6 mice were randomly administered one of three different antibiotics: ampicillin (25 or 50 mg/kg), cephalexin (60 or 120 mg/kg), or doxycycline (3 or 6 mg/kg). Ongoing pain behavior was assessed by an individual blinded to treatment group 30, 60, and 120 min following antibiotic administration via the mouse grimace score (MGS). All antibiotics caused small increases in MGS scores. Given these results, we next wanted to determine if dorsal root ganglia (DRG) neurons are directly activated by antibiotics. Antibiotics were applied to cultured mouse and human dorsal root ganglia (DRG) neurons for five minutes and resulting changes in intracellular calcium were measured. Mouse DRG neurons exhibited increases in intracellular calcium (49-87% of neurons responded) when exposed to amoxicillin (0.7-70 μg/mL), doxycycline (0.5-5 μg/mL), and azithromycin (0.04-4 μg/mL). However, 9% of human DRG neurons exhibited intracellular calcium flux upon exposure to amoxicillin. Interestingly, antibiotic-induced activity was attenuated in mouse DRG neurons incubated in calcium-free conditions, suggesting that extracellular calcium flux is necessary. These data support the hypothesis that clinically relevant doses of antibiotics induce acute ongoing pain in mice which may result from direct activation of DRG neurons.

Comparison Of cAMP-Dependent Signaling Pathways In Mouse Sensory Neurons And The HD10.6 Human Sensory Neuron-Derived Cell Line

Derek Molliver, Zaid Al-Abbasi; University of New England

Rodent dissociated dorsal root ganglion (DRG) neurons are used extensively for in vitro analyses of nociceptive signaling mechanisms, however there is concern that species differences can confound the clinical translation of potential drug targets identified in rodents. Although studies using live primary human DRG are becoming more prevalent, human tissue acquisition and use remain challenging. Human induced pluripotent stem cells (iPSCs) are a powerful alternative, but their phenotypes are very sensitive to culture conditions. Here, we used the human DRG-derived HD10.6 cell line to examine pro-nociceptive signaling pathways activated by cAMP downstream of Gαs protein-coupled receptors (GαsPCRs), including PKA, EPAC, PKC, and ERK. Transcriptomic analysis indicated that HD10.6 cells are reproducible and correlate well with primary human nociceptive neurons. Transcripts for diverse GPCRs expressed in human sensory neurons were identified in HD10.6 cells. Our findings reveal species-specific differences in cAMP signaling between mouse and human DRG models, employing a combination of electrophoretic and pharmacological methods. For instance, phosphorylated PKA and PKC substrate proteins revealed distinct profiles between models, with individual bands varying by species and GαsPCR agonists. Moreover, a PKA-selective cAMP analog induced ERK

phosphorylation (pERK) in HD10.6 cells but not in mouse DRG. Additionally, Epac1/2 inhibitors enhanced PKA activity in HD10.6 cells, suggesting PKA-EPAC crosstalk in human cells. In both species, GαsPCR agonist-induced pERK was largely dependent on EPAC-mediated PKC activation. The results reveal species differences in GαsPCR signaling, highlighting the importance of using human preclinical models to enhance our understanding of nociceptive signaling and develop effective pain therapeutics.Funding:R01NS109936.

Targeting the Insulin Signaling Pathway for the Treatment of Diabetic Peripheral Neuropathy

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Millions of people worldwide suffer from diabetic peripheral neuropathy (DPN), and current therapeutics are not completely effective for patients with DPN. In the present work, we explored the mechanistic underpinnings of insulin signaling to identify a potential therapeutic target for DPN in Type 1 Diabetes Mellitus (T1DM). We hypothesized that decreased insulin signaling through the IRS-1/PI3K/PIP3/AKT pathway in dorsal root ganglion (DRG) neurons would result in an increase in GSK3β activity and phosphorylation of tau, which would contribute to DPN in the Streptozotocin (STZ) model of T1DM. In these studies, mice were treated with a low dose (55mg/kg) of STZ for five days to induce T1DM. Von Frey, Thermal Gradient Ring, and Hargreaves tests were then to track mechanical and thermal sensitivity, which revealed the presence of mechanical sensitivity, but not thermal sensitivity. Histological analysis of the DRG four weeks after initiation of T1DM also revealed a significant increase in active GSK3β and p-tau within the neurons of STZ mice. To assess the potential of GSK3β as a target for DPN, we then treated STZ mice with the GSK3β inhibitor, Tideglusib, and found that mechanical sensitivity was significantly reduced in STZ treated mice. These results suggest that GSK3β could be an effective therapeutic target for treatment of DPN.Funding: NIH NIDDK(K99DK142197).

Single-Nuclei Ribonucleic Acid Sequencing Reveals Mechanosensitive and Inflammatory Drivers of Disc-Associated Chronic Low Back Pain

Sydney Caparaso, Ishwarya Sankaranarayanan, David Lillyman, Theodore Price, Rebecca Wachs; University of Nebraska-Lincoln

Chronic low back pain (LBP) is a leading cause of global disability. Up to 42% of patients have pain attributed to the intervertebral disc, termed disc-associated LBP. This condition features a catabolic disc microenvironment with altered mechanical loading, inflammation, and nociceptor innervation. Repeated nociceptor stimulation by mechanical and inflammatory stimuli induces plastic changes in dorsal root ganglia (DRG) neurons, including increased expression of ion channels and inflammatory markers. While these changes are well-documented in other pain conditions like osteoarthritis, their role in disc-associated LBP remains poorly understood, hindering development of effective treatments. Therefore, we developed a rat model of disc-associated LBP that replicates human-like disc degeneration and progressive pain-like behaviors.

DRGs (T13-L1) at 15 weeks post-injury (n=6 sham/injured) were analyzed using single-nuclei RNA sequencing, generating a transcriptomic atlas. Twelve transcriptomic clusters and 30,000+ differentially expressed genes were identified between injured and sham animals. Key findings include differential expression ($p \leq 0.05$) of Scn9a, Piezo2, Il6st, and Spock2, suggesting mechanosensitive and neuroinflammatory contributions to nociceptor plasticity. Il6st and Spock2 expression significantly correlated with axial hypersensitivity ($p \leq 0.05$), linking inflammation and extracellular matrix signaling to pain-like behavior. Rats treated with a mechanically stabilizing hydrogel showed a reduction in Piezo2 (7%) and Trpm8 (12%) expression (not statistically significant) and significantly reduced pain-like behavior ($p \leq 0.05$, weeks 13-15 post-injury) compared to injured controls. These findings suggest mechanical loading as a driver of pain. This work provides the first transcriptional map of DRG neurons in disc-associated LBP and informs future non-opioid therapeutic targets. Funded by NIH (NS065926, R01AR080926).

Spinal Interneurons Expressing Neuromedin U Receptor 2 Promote Neuropathic Pain
Tyler Nelson, Heather Allen, Olivia Davis, Theodore Price, Rajesh Khanna; University of Florida

Neuropathic pain is a significant clinical challenge with limited treatment options. Emerging evidence highlights glutamatergic interneurons in the superficial dorsal horn of the spinal cord as pivotal of neuropathic pain-induced allodynia. Using spatial transcriptomics, we identify a glutamatergic dorsal horn interneuron population, expressing Nmur2 (Neuromedin U Receptor Type 2), as a key mediator of neuropathic pain. Fluorescence in situ hybridization (FISH) confirmed that Nmur2-expressing interneurons co-localize with markers linked to pathological allodynia, including Sst and Npy1r, and that NMUR2 expression is conserved in the human dorsal horn. We then tested whether Nmur2-expressing interneurons are necessary and sufficientfor neuropathic pain-like behavior using in vivo chemogenetics and pharmacological approaches. Pharmacological or chemogenetic activation of Nmur2-expressing interneurons produced neuropathic pain-like behavior in uninjured mice. Conversely, chemogenetic inhibition of Nmur2-expressing interneurons abolished neuropathic pain-like behavior in mice with spared nerve injury (SNI). Additionally, chemogenetic inhibition of Nmur2-expressing interneurons reduced glutamatergic interneuron activity in the parabrachial nucleus in neuropathic but not un-injured states. Lastly, pharmacological antagonism of the neuromedin U receptor type 2 reduced inflammatory, neuropathic, and arthritic pain. These results highlight Nmur2-expressing interneurons and the neuromedin U receptor type 2 as promising therapeutic targets for the treatment of neuropathic pain.Funding: NIH awards K00NS124190, F32NS128392, RF1NS131165, R61NS126026, and R01NS120663.

PAR2 Antagonism Drug Delivery with Nanoparticles Block Nociception in Osteoarthritis Models
Marcella de Amorim Ferreira, Sher Poudel, Dane Jensen; New York University

Osteoarthritis (OA) is the most prevalent chronic joint disease, leading to locomotor restrictions and pain affecting the knee, fingers and temporomandibular joint (TMJ). The exact origin of pain in OA is not completely understood. The family of proteinase-activated receptors (PARs) are G

protein-coupled receptors (GPCRs) activated by proteases. PAR2, one of PAR family receptors, is expressed on inflammatory cells and sensory neurons where PAR2 has been linked to chronic joint inflammation and pain. PAR2 is also expressed on various joint structures like synovium, cartilage, and is activated by the protease cathepsin s, which is found in the synovial fluid. Herein, we investigate the role of PAR2 signaling in mouse models of OA and the potential of nanoparticle-facilitated drug delivery to block PAR2-mediated pain in OA. C57BL/6 mice received injections of iodoacetic acid in knee or TMJ to induce the OA models. To block PAR2, animals were treated with nanoparticles containing AZ3451 (AZ-NP), a PAR2 antagonist or empty nanoparticles intra-articular, 7 days after OA induction. Pain-related behaviors, including mechanical allodynia and spontaneous nociception were assessed. Intra-articular injections in knee and TMJ induced mechanical sensitivity in the ipsilateral paw and cheek from 1st until 14th days, with allodynia peaking at day 7. Seven days after intra-articular injections, we treated mice with AZ-NP to investigate the role of PAR2. The treatment with AZ-NP attenuated mechanical allodynia started 2 hours until 3 days after nanoparticles treatment. Our findings indicate that PAR2 can be a potential target utilizing new advancements in nanoparticles to treat OA.

Uncovering The Central Neural Mechanisms Underlying Sickness-Induced Hyperalgesia
Jacklyn Nguyen, Michelle Swarovski, Samuel Hedges, Jessica Osterhout; University of Utah

In response to infection, the brain generates stereotyped symptoms, including fever, fatigue, decreased appetite, hyperalgesia, and altered social interactions, ultimately promoting survival. Despite their critical role during an immune response, the neural basis for many sickness behaviors remains largely unknown. Hyperalgesia is a hallmark feature of infection. While much is known about how local inflammation can increase the excitability of nociceptive neurons, whether additional mechanisms are required for full-body hyperalgesia seen during systemic infection remains unclear. We recently uncovered a central humoral mechanism underlying the induction of select sickness symptoms through direct immune activation of neurons in the brain during systemic infection, suggesting that central immune sensitization may also play a key role in sickness-induced hyperalgesia. Using intraperitoneal injection of lipopolysaccharides (LPS) to model systemic infection, we identified a population of neurons in the ventral bed nucleus stria terminalis (vBNST) that are activated by LPS and noxious stimuli, suggesting a node at the intersection of pain and sickness. To test whether LPS-sensitive vBNST (vBNSTLPS) neurons are sufficient to generate pain responses, we utilized cre-dependent, viral-mediated functional manipulation to activate vBNSTLPS neurons. We found a significant impact on mechanical and thermal pain responses upon activation, indicating that vBNSTLPS neurons are sufficient to induce hyperalgesia. Single-nucleus RNA sequencing identified key markers for vBNSTLPS neurons and specific expression of immune receptors. Our results suggest that LPS-responsive neurons in the brain can mediate pain sensitivity and that central immune sensitization may play a key role in hyperalgesia and allodynia during sickness. Funding: R00NS114107.

Bombesin Receptor Subtype 3 Neurons In The Parabrachial Nucleus Facilitate Persistent Pain
Heather Allen, Tyler Nelson, Rajesh Khanna; University of Florida

Bombesin Receptor Subtype 3 Neurons In The Parabrachial Nucleus Facilitate Persistent PainHeather N. Allen1, Tyler S. Nelson1, Rajesh Khanna11. University of Florida, College of Medicine, Department of Pharmacology & TherapeuticsPersistent pain is a multifaceted experience that depends on supraspinal processing to integrate sensory and emotional signals. The parabrachial nucleus (PBN) is one of the first supraspinal regions to receive noxious input via the spino-parabrachial pathway. Painful stimuli increase activity of PBN neurons, and repeated activation of PBN neurons induces long lasting pain-like behavior. Recent transcriptomic studies and in situ characterization of PBN neurons identify neurons expressing Bombesin Receptor Subtype 3 (Brs3) as a subpopulation of interest for pain processing. Brs3 neurons express many well-known pain modulating GPCRs, including opioid receptors, tachykinin receptor 1, and neuropeptide Y Y1 receptors as well as high levels of the immediate early gene marker Fos after inflammatory pain. In vivo calcium imaging of Brs3 PBN neurons indicates increased activation in response to nociceptive stimuli after inflammatory pain compared to baseline. Further, activation of Brs3 PBN neurons produces spontaneous and evoked pain-like behaviors in otherwise naïve rodents. Finally, temporary inhibition or permanent genetic deletion of Brs3 neurons in the PBN reverses allodynia induced by the Complete Freund's Adjuvant model of inflammation. Ultimately, these findings suggest that parabrachial Brs3 neurons are involved in pain modulation and may provide a more precise target for understanding the supraspinal circuitry involved in inflammatory pain.Funded by F32NS128392.

Evaluating Arylepoxamide Receptor Agonist in Battlefield-Relevant Pain Models

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This study utilized two battlefield-relevant acute pain rat models of extremity trauma (ET) and thermal injury (TI) to evaluate the novel compound SBS1000 (Arylepoxamide receptor agonist (AEAr), Sparian Biosciences). The ET model was induced by crushing the right gastrocnemius and semimembranosus muscles for 30 sec with forceps and fibula fracture in anesthetized male Sprague-Dawley rats. TI was induced in anesthetized rats by placing a pre-heated metal probe (100oC) at the mid-plantar region of the hind paw for 30 sec. Three doses (0.1, 0.3, or 1 mg/kg) of SBS1000 was administered subcutaneously on either day 3 or day 7 post-injury (n=6/group). Control rats (n = 6/group) received vehicle (80% saline, 10% DMSO, 10% kolliphor EL). Effect of SBS1000 on mechanical allodynia and thermal hyperalgesia were measured at 90 min, 3- and 6- hrs. post-dosing. Following behavioral testing, the rats were humanely euthanized, and the right L4-L6 spinal cord was isolated followed by total protein isolation and a Luminex panel to measure the expression of inflammatory mediators. SBS1000 treatment significantly reduced mechanical allodynia and thermal hyperalgesia in the TI and ET rats. ET and TI resulted in a significant increase in several pro-inflammatory mediators which were significantly reduced with SBS1000 treatment. Our results indicate that AEAr agonist is an effective antinociceptive and anti-inflammatory agent in both ET and TI pain models. Identifying novel agents that can function on the battlefield as an analgesic with minimal side effects will greatly enhance the military's ability to effectively treat battlefield pain in future conflicts.

Sex-Specific Impaired Cholinergic Modulation In Prelimbic Cortex Following Spared Nerve Injury Model Of Neuropathic Pain

Soumil Dey, Yen-Hsin Cheng, Haram Kim, Marco Martina; Northwestern University

Acetylcholine serves as an essential neuromodulator in prefrontal cortex for attention, working memory and other cognitive tasks. Impaired cholinergic modulation is implicated in neuropathic pain-induced deactivation of prefrontal cortex. Differential genetic, molecular and systems-level mechanism of pain processing exist in male and female, but the detailed mechanisms of the sexual dimorphism are by and large not yet understood. Here we show evidence of sexual dimorphism in cholinergic modulation of mouse layer V commissural neurons of prelimbic cortex 1 week following peripheral nerve injury (SNI model of neuropathic pain). Commissural neurons were identified by injection of retrograde virus expressing a fluorescent tracer (mCherry) in the prelimbic cortex contralateral to the surgery and recording side. In contrast with the finding in the rat, patch clamp recordings in mouse slices showed that activation of cholinergic muscarinic receptors inhibits commissural neurons' excitability. This effect is mediated by M1 receptors in males and by both M1 and M2 receptors in females. 1 week after the peripheral lesion, cholinergic inhibition of commissural neurons was completely abolished in males. In female mice, however, the cholinergic inhibition remained virtually unaffected. These findings provide new evidence of sex-specific modulation of the mouse prefrontal cortex in neuropathic pain and suggests that this mechanism may contribute to the sexual dimorphism of cognitive impairment in neuropathic pain. (NIH RO1NS112292).

Sympathetic Neurotransmission Contributes to Oral Cancer-Induced Spontaneous Pain

Andre Martel Matos, Lisa McIlvried, Marci Nilsen, Megan Atherton, Nicole Scheff; University of Pittsburgh

Oral squamous cell carcinoma (OSCC) causes severe pain and stress, which exceed other cancers. We hypothesize OSCC progression drives sensory and sympathetic nerve injury, resulting in sympathetic-sensory coupled pain comprised of nociceptive spontaneous activity and adrenergic sensitivity. We prospectively accrued 100 OSCC patients (69.4±10, 65% male) for the assessment of patient-reported outcomes, circulating norepinephrine (NE), and tissue innervation. A syngeneic orthotopic tongue cancer mouse model (MOC2) was used with nociceptive behavior assays, calcium imaging, PCR, and immunohistochemistry to understand the mechanism for sympathetic-sensory nerve coupling. OSCC patients had 4-fold increase in platelet NE compared to healthy donors. Spontaneous pain positively correlated with circulating NE ($r=0.634$). Sympathetic nerves identified by tyrosine hydroxylase (TH) comprised 4.73±1.3% of total nerve density in resected tumors and there was a positive correlation ($r2=0.309$) between TH and spontaneous pain. We recapitulated the patient phenotype using the MOC2 mouse model; mice had spontaneous pain and intratumoral sympathetic and sensory innervation. Evaluation of tongue innervating sensory trigeminal neurons (TGN) revealed a significant increase in ATF3 and Adra1 expression in cancer mice suggesting injury-induced excitatory adrenergic sensitivity. Functionally, NE evoked a $Ca2+$ transient in dissociated TGNs from cancer mice (91%) compared to sham (9%). Local chemical ablation of sympathetic innervation improved pain behaviors and attenuated peripheral nerve injury. Local chemical denervation of

TRPV1-expressing TGNs ameliorated pain behavior and reduced NE release by 75.4±16% in the tumor. These results suggest tumor-induced nerve injury may drive sympathetic-sensory nerve coupling, resulting in a significant sympathetic component of oral cancer pain.

Selective Activation of Protease-Activated Receptor 2 Induces Hyperexcitability in Human Dorsal Root Ganglion Neurons

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Migraine is the most disabling neurological disorder worldwide and is likely governed by multiple physiological mechanisms. Activation of protease-activated receptor 2 (PAR2) has been identified as a robust contributor to migraine-like behavior in mouse models. PAR2 is expressed in 3-4% of murine sensory neurons. However, PAR2 is expressed in >30% of human sensory neurons, and this discrepancy likely results in an underestimation of the role of PAR2 in human migraine and other pain disorders. We used patch-clamp electrophysiology to examine effects of PAR2 activation on excitability of dissociated human dorsal root ganglion neurons. Cells were treated with PAR2 activators including the selective agonist 2at-LIGRL-NH2 as well as elastase, an endogenous protease that activates the receptor. Spontaneous activity, rheobase, and action potential frequency were measured. Additionally, cells were pre-treated with PAR2 antagonists prior to PAR2 activators and the same excitability measures were determined. We found that cells treated with PAR2 activators were hyperexcitable; there were more spontaneously active neurons in the treatment groups, cells had lower rheobase, and fired more action potentials than controls. These effects could be completely blocked by pre-treatment with a selective PAR2 antagonist. These data indicate that both selective and physiological PAR2 activators induce hyperexcitability of human dorsal root ganglion neurons and these effects can be fully blocked with PAR2 antagonism. This work establishes that PAR2 activation signals to mechanisms that cause hyperexcitability in human sensory neurons and further supports the rationale for investigating PAR2 as a target for treating pain and migraine in humans.

A Potential Role Of Central Circuits In Female Specific Light Aversion.

Agatha Greenway, Brandon Rea, Jayme Waite, Levi Sowers; University of Iowa

Migraine is a prevalent female dominant neurological disorder. Previous work has implicated CGRP neurons of the medial nucleus (MN) of the cerebellum in a female specific light aversive phenotype in mice upon optogenetic stimulation. We were interested in the downstream targets of this female specific phenotype. The MN projects to the anterior cingulate cortex (ACC) via the mediodorsal thalamus. Human fMRI studies have demonstrated increased activation of the ACC in the premonitory and headache phase of migraine, but there are few migraine behavioral studies focused on the ACC. We wanted to determine if optogenetic stimulation of the ACC is sufficient to induce migraine like phenotypes in mice.Channel rhodopsin-2 with expression driven by CamKIIα was injected into the right ACC, and a fiber optic probe was implanted directly above the viral injection site 3 weeks prior to behavioral testing. We use behavioral assays to model migraine like behaviors in mice including the light dark assay (measuring light aversion as a surrogate for photophobia), the plantar von Frey assay (touch hypersensitivity as a

surrogate for extracephalic allodynia), automated squint (spontaneous pain), and a variety of mazes that measure anxiety and cognition.Here we show that there is a trend towards a light aversive phenotype in the experimental group that is driven by a significant female specific light aversive phenotype. These results are similar to the MN, and moving forward we hope to probe the MN to ACC projection which could reveal a potential therapeutic target for migraine.

Unlocking the Gut-Brain Connection: Targeting the Microbiome to Relieve Visceral Hypersensitivity and Restore Function in Irritable Bowel Syndrome

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Disorders of gut-brain interactions (DGBIs), including irritable bowel syndrome (IBS), rank among the most common gastrointestinal disorders, marked by recurrent abdominal pain and altered bowel habits in the absence of structural disease. Current IBS treatments provide limited pain relief, primarily addressing symptoms rather than targeting the underlying pathophysiology. Visceral hypersensitivity (VH), heightened sensitivity to bowel distention, is a key peripheral factor driving pain in DGBIs, yet remains poorly understood. Recent studies suggest a link between gut microbiome dysbiosis, intestinal permeability, and visceral hypersensitivity (VH), but it remains unclear if these changes drive or result from IBS. We have previously identified specific differences in gut microbial colonization between VH-susceptible C57BL/6NTac (BL/6NTac) and VH-resistant (C57BL/6J) mice in a zymosan (ZYM)-induced IBS model, with VH-susceptible mice exhibiting Firmicutes (Bacillota) enrichment, specifically Lachnospiracaea Dorea, similar to findings from IBS patients. To further understand how the microbiome plays a role in ZYM-VH, we developed and validated an antibiotic (ABX) treatment protocol followed by a fecal microbiota transplant (FMT). Transplanting fecal supernatant from ZYM-VH mice into naive mice caused visceral hypersensitivity, increased colonic Tlr2 expression indicative of elevated immune response, and increased intestinal permeability. We are currently investigating whether selective reduction of bacteria associated with IBS phenotype can restore normal gut function and promote recovery. Using the ZYM-IBS mouse model, we are using targeted antibiotic treatment to see if we can reverse key symptoms like pain, intestinal dysfunction, and increased intestinal permeability. These findings support microbiome-targeted interventions as a promising approach for managing VH in IBS.

Identification of Cocaine- and Amphetamine-Regulated Transcript (CART) Expression in Waldeyer Marginal Zone Spinothalamic Projection Neurons: Potential Implications for Human Pain Transmission

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Understanding the molecular profile of dorsal spinal cord projection neurons, which relay nociceptive signals to the brain, is key to uncovering pain processing mechanisms and identifying potential pain management targets. Our study reveals the expression of the cocaine-

and amphetamine-regulated transcript (CARTPT) gene in a distinct population of large dorsal horn "Waldeyer" neurons, suggesting a novel role in pain signaling alongside its known involvement in reward and addiction. We designed a custom probe set of 300 genes using Xenium spatial transcriptomics to profile the gene expression of spinal projection neurons. Waldeyer neurons were primarily localized to the marginal zone (lamina I) of the dorsal horn and co-expressed several pain-related peptides and receptors, including tachykinin 1 (TAC1, encodes substance P), cholecystokinin (CCK), and the mu-opioid receptor (OPRM1). Additionally, these neurons express glutamatergic transmission components, including NMDA receptor subunit 1 (GRIN1) and AMPA receptor subunit 4 (GRIA4). While most CARTPT-expressing neurons were found in lamina I, some were observed in the overlying white matter and deeper spinal laminae. These findings were confirmed with multiplex fluorescence in situ hybridization and immunohistochemistry, which demonstrated the presence of CARTPT mRNA and CART protein in Waldeyer neurons. Notably, the identification of CART in these neurons is human-specific, as it has not been observed in rodent lamina I neurons. These results suggest that CART may play a novel role in ascending nociceptive processing, and future studies will explore the spatial distribution of CART-containing terminals in the pontine parabrachial nucleus and thalamic mediodorsal and ventroposterolateral nuclei.

Neuropilin-1 Interplay with Nerve Growth Factor Contributes To Sustaining Periorbital Pain

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Nerve Growth Factor (NGF) and its receptor, tropomyosin receptor kinase A (TrkA), play crucial roles in pain mediation and are implicated in various painful disorders (Denk, 2017). Despite their significance, clinical trials involving NGF-targeting monoclonal antibodies for chronic pain have been halted due to adverse effects, the mechanisms of which remain unclear (Hochberg, 2016). Neuropilin-1 (NRP1) is a transmembrane protein co-receptor for multiple ligands and receptor tyrosine kinases but does not have direct signaling capabilities (Rizzolio, 2012; Gomez, 2023). Given NGF's involvement in pain and its potential binding motif for NRP1, we propose that NRP1 acts as a critical co-receptor for NGF/TrkA, playing a crucial role in periorbital pain induced by NGF or supernatant from human tongue squamous carcinoma cells (HSC-3). Using RNAScope, we demonstrated that the mRNA for TrkA and NRP1 are co-localized in mouse trigeminal ganglion (TG) neurons. Through pharmacological, biological, and genetic antagonists of NRP1, we found that NRP1 is a necessary co-receptor for the periorbital mechanical allodynia induced by NGF or HSC-3 supernatant. TrkA activation phosphorylates proalgesic receptors, such as the Transient Receptor Potential Vanilloid 1 (TRPV1), amplifying NGF-induced pain signaling (Zhu, 2007). To validate NRP1 as a potential co-receptor for NGF/TrkA, we assessed its contribution to the intracellular effects mediated by NGF/TrkA activation using calcium imaging of mouse TG neurons. Our findings show that NRP1 antagonists reduced the sensitization of TRPV1 induced by NGF or the supernatant, supporting that NRP1 mediates the pronociceptive actions of NGF/TrkA in mouse TG neuron's signalling capabilities.

A Synthetic Potassium Channel Reduces Oxidative Stress Via Cellular Adaptronics

Rajesh Khanna, Alberto Russo, Andrea Saponaro, Simone Trini, Tyler S. Nelson, Heather N. Allen, Rebecca Oddone, Chiara Villa, Yvan Torrente, Alessandro Porro, Gerhard Thiel and Anna Moroni, University of Florida

Aerobic metabolism is crucial for human life but reactive oxygen species (ROS) byproducts cause cellular toxicity. Although antioxidant defenses usually maintain ROS levels within a safe range, ROS production can exceed the buffering capacity of cells, causing oxidative stress and disease. Inspired by the principle of adaptronics, we created a synthetic potassium channel that senses cellular ROS levels and mitigates oxidative stress by modulating membrane potential. Engineered from TASK1 channel, ROSTASK1 is sensitive to supraphysiological ROS levels, imposing restorative membrane potential changes on cells or organelles under oxidative stress. We also engineered a blue-light sensitive ROSTASK1 to achieve optogenetic control. In proof-of-concept experiments, mitochondrially-delivered ROSTASK1 rescued ROS overproduction in myoblasts from a Leigh syndrome patient and ROSTASK1 abolished chronic pain-like behavior in mouse models of inflammation and nerve injury. Thus, by functioning as both a sensor and modulator of ROS levels, ROSTASK1 provides a self-healing system during oxidative stress.

Characterizing the Symptomatic and Joint-Level Consequences of Comorbid Hypertension and Osteoarthritis in Male and Female Rats

Carlos Cruz, Folly Patterson, Janak Gaire, Jacob Griffith, Kyle Allen; University of Florida

Osteoarthritis (OA) is a painful disease that commonly presents with comorbidities such as hypertension. The prevalence of OA is greater with hypertension, even after controlling for BMI (Lo et al., 2022). Hypertension can also influence pain sensitivity, complicating the relationship between symptoms and OA progression. Understanding how hypertension influences OA symptoms is critical since pain is a primary motivator for seeking OA treatment. Here, we measured pain-like behaviors (gait and tactile sensitivity) in spontaneously hypertensive rats and Sprague-Dawley rats (normotensive) at baseline, 4-, and 8-weeks post induction of OA. OA was induced in the right stifle (knee) joint via transection of the medial collateral ligament and medial meniscus; skin incision was used as our sham control. Endpoint histology assessed joint damage and subchondral neurovascular changes. Prior to OA, hypertensive rats walked with an abnormal gait (shorter strides, decrease in vertical load) compared to normotensive rats, regardless of sex. By week 8, hypertensive-OA females developed an antalgic (limp) gait, which was not observed in other groups or males. Hypertensive-OA rats showed greater cartilage loss than normotensive-OA rats, with females developing larger osteophytes and greater CD31+vasculature in the subchondral bone plate. No differences in tactile sensitivity were observed. Overall, hypertension worsened joint damage in OA, with more pronounced joint remodeling and gait compensations observed in females. Ultimately, this work shows that hypertension exacerbates OA pathogenesis and encourages future work focusing on sex differences and vascular changes as potential physiological roots. NIH (R01AR071431 and R01AR071431-03S1).

GsMTx-4 as a Blocker of Schwannomatosis Tumor Pain

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Patients with schwannomatosis (SWN) develop multiple tumors along major peripheral nerves, with most experiencing significant pain, though each patient's symptoms are unique. Neuropathic, nociceptive, and inflammatory pain types have been reported, but many patients describe severe pain when a schwannoma is palpated or even lightly touched. Currently, the only effective treatment for pain relief is surgical removal. We are investigating the root causes of tumor-induced pain. In some cases, tumor growth increases pressure on nearby nerves, resulting in pain. Additionally, schwannoma cells in culture secrete proinflammatory cytokines into the surrounding medium. This conditioned medium (CM) sensitizes sensory neurons to painful stimuli both in vitro and in vivo. When injected into the glabrous skin of a mouse hindpaw, CM from painful schwannomas increases sensitivity to light touch, as demonstrated by a fourfold reduction in paw withdrawal threshold (measured using the Von Frey assay) one hour post-injection ($p = 0.006$), with effects persisting for 24 hours ($p = 0.002$). We hypothesize that this increase in mechanosensitivity is linked to mechanosensitive ion channels (MSCs), which detect pressure and stretch. These channels can be blocked by the peptide GsMTx-4, which penetrates into cell membranes under mechanical pressure to block MSCs from opening without affecting other ion channels. When co-injected with CM into the mouse hindpaw, 10 μM GsMTx-4 prevents the heightened sensitivity to light touch. Moreover, GsMTx-4 can reverse hyperalgesia, restoring withdrawal thresholds to baseline levels. Thus, local injection of GsMTx-4 near painful tumors presents a promising, minimally invasive therapeutic approach for SWN patients.

Single-Cell Comparison of Microglia Across Brain Regions, Species, and Neurodegenerative Diseases

Wei Feng, Guoyan Zhao; Washington University School of Medicine

Neurodegenerative diseases (NDs) such as Alzheimer’s disease (AD), Parkinson’s disease (PD), and Huntington’s disease (HD) are characterized by pathological protein aggregation and deposition, which trigger the activation of microglia. The activation of these brain-resident immune cells is also closely linked to chronic pain conditions, as microglia-mediated neuroinflammation can exacerbate pain signaling in both disease and injury contexts. However, understanding the roles of microglia in NDs and pain is challenging due to the heterogeneity of microglial subpopulations and variations across tissues, diseases, and analytical methods.To address this, we analyzed nine human snRNA-seq datasets from diverse brain regions and ND conditions, identifying two conserved microglial subpopulations between humans and mice. Extending the analysis to include additional brain regions and disease conditions in thirteen mouse snRNA-seq datasets, we confirmed heterogeneous microglial responses and identified shared genes and pathways across species. Differential expression analysis revealed species-specific dysregulated genes, underscoring the complexity of microglial activation.This study provides insights into conserved and divergent microglia genes and pathways, with implications for understanding their roles in both neurodegeneration and pain. By highlighting the translatability of mouse models to human conditions, this work advances efforts to develop microglia-based therapies for alleviating neuroinflammation-associated pain.

Effects of Diet On Cancer Outcomes and Pain in Mice

Stacie Totsch, Lyse Norian, Robert Sorge; University of Alabama at Birmingham

The majority of women diagnosed with ovarian cancer experience disease-related pain that is often exacerbated by treatment. It is estimated that roughly 56% of women with newly-diagnosed ovarian cancer received chemotherapy within 1 year, suggesting that a substantial portion of women may be suffering with cancer-associated pain prior to traditional cancer therapies. Nutrient-dense diets are associated with improved cancer-related outcomes and quality of life. However, little is known about the relationship of cancer, diet, and pain. Here we investigated the interaction between cancer progression, our plant-based nutrient-dense, anti-inflammatory diet (AID), and pain in a murine model of ovarian cancer. Tumor-bearing mice exhibited mechanical hypersensitivity within one week of tumor administration that persisted throughout the duration of the experiment. AID-consuming mice exhibited less sensitivity compared to standard chow-consuming mice. Live in-vivo bioluminescent imaging revealed that prophylactic AID (4 weeks prior to cancer induction) decreased tumor progression. Outcome measures including ascites volume, omental weight, and body circumference were also reduced in AID-consuming animals. Additionally, nanostring analysis of excised tumors revealed differential gene expression of 20 genes between AID-consuming mice and chow-consuming mice. Thus, our data support the use of an anti-inflammatory diet to mitigate tumor progression and improve outcome measures. Of note, our nanostring data provide support for future mechanistic studies identifying therapeutic targets. The non-toxic, safety profile of our dietary intervention can be rapidly moved from bench-to-bedside for ovarian cancer patients. Funded by the Norma Livingston Ovarian Cancer Foundation.

Protective Effects of Ozanimod in Cisplatin-Induced Neuropathic Pain in Mice: Insights From Single-Cell Transcriptomic Profiling in Spinal Cord Tissues

Ying Li, Rachel Schafer, Silvia Squillace, Luigino Giancotti, Terrance Egan, Stella Hoft, Richard DiPaolo, Daniela Salvemini; Institute for Translational Neuroscience, and Saint Louis University School of Medicine

Chemotherapy-induced peripheral neuropathy accompanied by neuropathic pain (CINP) is a major neurotoxicity of cisplatin, a platinum-based drug widely used for lung, ovarian, and testicular cancer treatment. CINP causes drug discontinuation and severely impacts life quality; there are no FDA-approved interventions. We have previously reported that platinum-based drugs increase levels of the sphingolipid, sphingosine 1-phosphate (S1P) in the spinal cord and drive CINP through activation of the S1P receptor subtype 1 (S1PR1). However, the cellular and molecular mechanisms engaged downstream of S1PR1 remain poorly understood. Our single cell transcriptomics on mouse spinal cord uncovered subpopulation-specific responses to cisplatin. Particularly, cisplatin increased the proportion of astrocytes with high expression levels of S1pr1 (S1pr1high astrocytes), within which cisplatin upregulated the Fgfr3-included Wnt signaling. Notably, the fibroblast growth factor receptor 3 (FGFR3) encoding gene Fgfr3 showed an identical expression pattern to S1pr1 in astrocytes subpopulations. Cisplatin-induced upregulation of Wnt signaling and neuropathic pain were prevented by ozanimod, a functional antagonist of S1PR1. Moreover, intrathecal injection of PD173074, a FGFR3 antagonist, prevented the development of cisplatin-induced neuropathic pain. These data highlight FGFR3 as one of the astrocytic targets of S1PR1 in response to cisplatin. Similar analysis in microglia revealed FKBP5 (FK506 binding protein 51) as a potential downstream microglial target of

S1PR1.Overall, our results provide a comprehensive mapping of cellular/molecular changes engaged by cisplatin in neuropathic pain and deciphers novel glial-based mechanisms of action engaged by S1PR1. This study was funded by SLU discretionary startup funds and the NIH grant R01CA261979 (DS).

Loss of Environmental Enrichment Induces Prolonged Pain Behaviors After Ischemia with Reperfusion Injury and Transcriptomic Changes in Satellite Glial Cells.
Lindsey Preece, Anna French, Luis Queme, Mathew Magyar-Ng; University of New England

About 20% of US adults experience chronic pain at least once in their lifetime. Stress has been associated with increased incidence of chronic pain and the development of post-surgical pain. Nevertheless, the mechanisms behind how stress may influence the development of chronic pain are still unclear. Satellite Glial Cells (SGCs) are support and envelop sensory neurons in the Dorsal Root Ganglia (DRGs) and have been implicated in the development of musculoskeletal pain in conditions such as fibromyalgia. Recently, we developed a mouse model of chronic stress, based on loss of environmental enrichment (LoE) and paired it with a model of hindlimb muscle ischemia with reperfusion injury (I/R) to study the effects of stress on the development of chronic musculoskeletal pain. We hypothesized that LoE would induce mechanical hypersensitivity and that this would correlate with increased activity and transcriptomic changes SGCs. To test this, we exposed animals to our LoE stress paradigm and after one week performed an I/R on the right hindlimb. We observed mechanical hypersensitivity after LOE that got exacerbated after I/R that did not recover in the animals exposed to LoE, that correlated with increased GFAP signal in the DRG. RNAseq from SGCs isolated from mice exposed to I/R, with and without stress, showed a significant upregulation in several genes, including a sexually dimorphic upregulation of CX3CR1, the receptor for Fractalkine, a chemokine associated with the development of neuropathic pain. These findings suggest that LoE may facilitate the development of chronic pain through a SGC-dependent mechanism.

Studying the Interplay of Estrogen with its Receptors ERa, ERb, and GPER with Porcine Coronary Arteries and Bovine Endothelial Cells
Deesha Patel, Connor Hayes, Guichun Han; Kentucky College of Osteopathic Medicine

Cardiovascular disease remains the leading cause of death in the United States, particularly affecting post-menopausal women due to diminished estrogen levels. While hormone replacement therapy (HRT) has been proposed to mitigate this risk, the Women's Health Initiative (WHI) study raised concerns about its association with increased heart attack and stroke incidence in older women. However, the North American Menopause Society suggests that HRT may still be beneficial if initiated before age 60. This study aims to elucidate the roles of estrogen receptors ERα, ERβ, and GPER in coronary artery relaxation using isometric tension studies in porcine coronary arteries. We hypothesize that GPER plays a critical role in mediating the relaxation induced by ERα and ERβ. Fresh porcine hearts will be used to isolate coronary artery rings, contracted with PGF2α, and subjected to treatments with estrogen (E2), GPER agonist G-1, ERα agonist PPT, and ERβ agonist DPN. The roles of the receptors will be investigated using siRNA knockdown and receptor-specific antagonists, alongside western

blotting for protein expression verification. We anticipate that E2 will demonstrate the most significant relaxation effect on PGF2α-induced contraction, primarily through eNOS activation and NO release. The individual effects of ERα and GPER agonists are expected to be less pronounced due to the lack of synchronized receptor interaction. This research aims to enhance understanding of HRT's efficacy and safety, potentially leading to targeted strategies against cardiovascular disease in women, particularly during late menopause.

Sphingosine-1-Phosphate Receptor-1 Functional Antagonism Attenuates Morphine-Induced Osteolysis and Hyperalgesia in a Murine Model of Metastatic Breast Cancer
Nikhil Mathur, Maha Sulaiman, Mathew Repp, Rorie Robinson, Tally M. Largent-Milnes,Todd W. Vanderah; University of Arizona College of Medicine
Breast cancer has a high propensity to metastasize to the bone and is frequently accompanied by a diminished quality of life. Most women with advanced breast cancer suffer from substantial cancer-induced bone pain (CIBP) requiring escalating doses of opioids for relief. However, these treatments lack long-term effectiveness due to analgesic tolerance, opioid-induced hypersensitivity, and recent associations with bone loss. The molecular mechanisms behind these adverse effects remain unclear. Using a non-immunocompromised murine model of metastatic breast cancer, we found that chronic treatment with a mu-opioid agonist, an analgesic for metastatic chronic cancer pain, significantly increases osteolysis and hyperalgesia in the ipsilateral femur. Concurrently, adding a Sphingosine-1-Phosphate Receptor-1 (S1PR1) functional antagonist may reverse the unwanted effects of opioids, potentially transforming treatment for metastatic cancer patients. Our previous studies show that Sphingosine-1-Phosphate (S1P) levels rise in metastatic cancer and that S1PR1 inhibition attenuates proinflammatory cytokines/chemokines. Yet, outside our research, little is known about the S1PR1 system in bone cancer. Here, we investigate and validate that inhibiting S1PR1 activation using the clinically approved antagonist FTY720 (fingolimod, Gilenya®) combined with standard opioid treatment significantly inhibits pain and bone degradation in a murine model of bone cancer pain. This data indicates that sustained morphine induces osteolysis and hyperalgesia, and that S1PR1 antagonism in a murine metastatic breast cancer model can prevent bone loss while significantly inhibiting bone cancer pain.

Clinical and/or Translational Research

Clinical and Cytokine Predictors of Persistent Post-Operative Pain in Older Adults
L. Savannah Dewberry, Mary Cooter Wright1, Marguerita Klein, Michael Devinney, Miles Berger, Andrea Nackley; Duke University

Chronic postsurgical pain (CPSP) affects 10-50% of individuals. This study analyzed 110 adults ≥60 years old undergoing non-neurologic, non-cardiac surgeries to identify risk factors for CPSP. Pain (VAS), depression, and anxiety were assessed at baseline and 1 year post-surgery. Plasma and cerebrospinal fluid (CSF) samples were collected at baseline, 24 hours, and 1 year. CPSP (VAS >3.5) was observed in 28 (25.5%) patients at 1 year. Patients with chronic primary pain conditions (CPPCs) were more likely to have CPSP ($p=0.02$). Baseline anxiety was positively correlated with higher 1-year pain scores ($r=0.184$, $p<0.05$), and in patients with CPPCs, baseline

pain and anxiety interaction was associated with higher 1-year pain ($p<0.05$). Overall, greater 24-hour increases in plasma IL-7, TNF-β, and IL-16 were negatively associated with 1-year pain scores; however, in the subset of patients with CPPCs greater 24-hour increase in plasma IL-7, IP10, and TARC were positively associated with 1-year pain scores. TNF-β maintained a negative association with 1 year pain in the CPPC subgroup. No CSF biomarkers were associated with 1-year pain in patients without CPPCs, but in those with CPPCs, 24-hour postoperative increases in IL-10, IL-8, MCP-1, GROα, and MCP-2 were negatively associated with 1-year pain. These findings suggest that robust early inflammatory responses may aid pain resolution in non-CPPC patients but exacerbate pain in those with CPPCs. Baseline anxiety and CPPC status influence CPSP risk, emphasizing the importance of tailored interventions.

Photophobia in Chronic Ocular Pain: Links to Ocular Symptoms and Signs
Ema Karakoleva, Nicholas Pondelis, Cameron Talbert, Mariela Aguilar, Alex Gonzalez, Heather Durkee, Paula Sepulveda Beltran, David Valdes, Chloe Shields, Shreya Bhatt, David Zurakowski, Deborah Jacobs, Joseph Ciolino, Elizabeth Felix, Jean-Marie Parel, Eric Moulton, Anat Galor; Bascom Palmer Eye Institute

Photophobia in Chronic Ocular Pain: Links to Ocular Symptoms and SignsEma Karakoleva, Nicholas Pondelis, Cameron Talbert, Mariela Aguilar, Alex Gonzalez, Heather Durkee, Paula Sepulveda, David Valdes, Chloe Shields, Shreya Bhatt, David Zurakowski, Deborah Jacobs, Joseph Ciolino, Elizabeth Felix, Jean-Marie Parel, Eric Moulton, Anat GalorBascom Palmer Eye Institute, University of Miami, Miami, FL, USAPhotophobia, or painful light sensitivity, is a prevalent yet poorly understood symptom that can significantly impact quality of life, particularly among individuals with chronic ocular pain (COP). This cross-sectional study quantified visual photosensitivity thresholds (VPT) using a novel device (the Ocular Photosensitivity Analyzer) in 36 COP patients (average eye pain ≥1 over past week, duration ≥3 months) and 39 controls without eye pain. Ocular symptoms were captured with the Ocular Surface Disease Index [OSDI,0-100], Neuropathic Pain Symptom Inventory-modified for the Eye [NPSI-E,0-100], and Visual Light Sensitivity Questionnaire-8 [VLSQ-8,8-40]. Ocular surface signs included tear breakup time, Schirmer test, and corneal staining. COP patients (39.2+/-15.6yo, 56%Female) had significantly lower VPT (1.60+/-1.17 vs.2.42+/-1.05 loglux,$p=0.002$) compared to controls (46.5+/-15.6yo, 56%Female). NPSI-E Question 9, quantifying photosensitivity severity (0-10), was most strongly correlated with VPT ($r=-0.73$,$p<0.001$). OSDI and VLSQ-8 also showed negative correlations with VPT ($r=-0.41$ and -0.69, respectively, both $p<0.01$) among COP subjects. No significant correlations were observed between ocular symptoms and VPT in controls, all of whom had low symptom burden. Ocular surface metrics were not correlated with VPT in either group. Our findings suggest that ocular symptoms, rather than signs, correlate more closely with photosensitivity among COP patients.(Funding:U01EY034686).

Assessment of Visual Sensory Responsiveness Associated with Nociplastic Pain in Knee Osteoarthritis
Tony Larkin, Poonam Purohit, Anne Arewasikporn, Chelsea Kaplan, Chad Brummett, Andrew

Schrepf, Daniel Clauw, Steven Harte; University of Michigan Health System Chronic Pain and Fatigue Research Center

Knee osteoarthritis (OA) is characterized by joint degeneration, pain, stiffness, and reduced physical function. However, for many individuals with knee OA, the association between the degree of joint damage and self-reported pain intensity at the knee is poor, suggesting central nociplastic mechanisms may be driving or contributing to pain in these individuals. Cardinal nociplastic features include widespread pain and increased sensitivity to environmental stimuli (e.g., lights, odors). To examine potential nociplastic mechanisms in knee OA, the spatial extent of pain across the body and sensitivity to non-painful visual stimuli were evaluated in twenty-two individuals (mean age = 64.64 ± 6.99 years, 45.5% female) awaiting knee arthroplasty. Participants completed the Michigan Body Map to identify the presence of pain in seven distinct body regions. Pain in any site within a region counted toward an index score; participants with an index score of 3 or higher indicated widespread pain, whereas scores less than 3 were classified as no/regional pain. Visual sensitivity was assessed using a flashing checkerboard presented at six illumination levels (4.5-76 lux). Participants rated perceived brightness and sensory unpleasantness after each stimulus presentation on a 0-100 numerical rating scale. Statistical analyses compared group differences between participants with widespread pain vs. those with no/regional pain. The widespread pain group (n=11) perceived the visual stimulus as brighter (p=0.04) and more unpleasant (p=0.06) compared to the no/regional pain group (n=11). These findings suggest a subgroup of individuals with knee OA exhibit widespread pain and heightened sensory responsiveness, features of nociplastic pain.

Title: Proof of Concept Study to Determine the Effectiveness and Safety of Oral Topical Application of Resiniferatoxin for the Control of Pain Associated with Feline Chronic Gingivostomatitis (FCGS)

Snigdha Chigurupati, Matthew Sapio, Alexis Namaha, Alvaro Cisternas, Michael Iadarola, Andrew Mannes; National Institutes of Health

Feline Chronic Gingivostomatitis (FCGS) is a prevalent veterinary condition often used to model human immune-mediated oral mucosal diseases, such as radiation-induced oral mucositis (OM). To investigate a novel non-opioid analgesic modality to address OM, we conducted a non-randomized, unmasked, multi-center proof-of-concept study to assess the safety of resiniferatoxin (RTX) in managing oral pain in 28 client-owned cats with FCGS. Cats exhibiting FCGS symptoms significantly impairing quality of life for at least three months were divided into three cohorts based on RTX doses (6.25, 12.5, or 25 μg). In addition to safety, efficacy was preliminarily measured at different time points over a 28-day period post-RTX administration, utilizing the Veterinarian Specific Outcome Measures (VSOM) and Stomatitis Disease Activity Index (SDAI) scales as well as each cat's ability to eat. Treatment success was defined as a reduction of at least 2 points in VSOM scores and a 20% reduction in SDAI scores at day 28 compared to day 0. Success rates for VSOM on day 28 were 90%, 80%, and 88.9%, and for SDAI were 100%, 80%, and 44.4% across the 6.25 12.5, and 25 μg cohorts, respectively. Further, there was an improvement in ability to eat by day 28 for all three cohorts. Regarding safety, most adverse events were mild or moderate with only two severe events of oral pain, effectively managed with analgesics. Overall, this study highlights RTX's favorable safety

profile while also providing preliminary evidence for its analgesic and anti-inflammatory wound healing properties.

Strategies For Communicating With Participants To Enhance Study Initiation And Retention In A Pragmatic Clinical Trial

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The purpose of this study was to enhance rates of initiation and retention of participants in the pragmatic clinical trial Fibromyalgia TENS in Physical Therapy Study (FM-TIPS). The goal of FM-TIPS is to determine whether the addition of TENS to physical therapy helps patients with FM to move with less pain. Participants were enrolled directly through their physical therapist at 25 clinics throughout the Midwest. Participants completed informed consent and data collection surveys (homework) at home through Research Data Capture (REDCap) on their personal devices. Text messages and emails were sent to eligible participants automatically through REDCap alerting them to their study status and providing the link for the Informed Consent Form (ICF) and subsequently the first study homework (HW day 1). Clinicians were trained to encourage and check for completion of study activities through HW day 1. Homework was repeated at days 30, 60, 90, and 180. To alert participants to complete homework, email and text message reminders were sent automatically through REDCap at three timepoints during the 11 days the surveys were open. As the study progressed, we implemented personal phone calls, emails, and texts to further encourage completion of study activities. Weekly interaction was implemented through HW 1 completion and up to daily during the last 4 days of the HW completion windows. These interactions also encouraged participants to contact the study when they encountered problems with the technology and study devices.

Further Support for FKBP51 as a Therapeutic Target for Chronic Posttraumatic Pain

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Patients with chronic pain often report a traumatic stress exposure (TSE) that triggered the pain onset. While many survivors report for care following TSE, few interventions are available to prevent chronic pain in these individuals. Therefore, novel therapeutic strategies are needed. We previously showed that genetic risk variants in a key regulator of the stress system, FKBP5, are associated with worse chronic pain outcomes in TSE survivors and that pharmacological inhibition of the corresponding protein (FKBP51) in stressed rats prevents hypersensitivity. In response to NIH/HEAL initiative calls for increased validation of novel pain targets, as well as safety testing, this study aimed to further explore FKBP5/FKBP51 as a safe and effective novel pain target. In humans, we used data from AURORA, a longitudinal cohort study of multiethnic men and women who experienced TSE (n=2,387), to test whether FKBP5 risk alleles predict post-TSE chronic pain. We found a statistically significant association between the number of

FKBP5 risk alleles and moderate (β=0.27, p=0.007) or high (β=0.41, p=0.0002) unremitting pain. In cross-species/lab validation analyses, mice experienced less mechanical hypersensitivity following TSE when inhibiting FKBP51 (F(1,14)=13.17, p=0.003). Further, FKBP51-inhibition augmented post-TSE activity (measured via radiotelemetry) in rats. Finally, in pharmacological inhibition experiments in rats, conditioned place preference showed an absence of abuse liability and arrhythmogenesis was not detected via ECG nor RT-qPCR of arrhythmogenic genes. These studies further implicate FKBP51 as a promising therapeutic target for post-TSE chronic pain. Future studies are needed to continue to validate the safety and efficacy of this target.

Can We Treat 100 Individuals at Once? Online 1-Session Empowered Relief in a National Sample of Marfan Syndrome and Related Disease

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Between 50% and 90% of individuals with Marfan syndrome and related connective tissue conditions experience chronic pain. We conducted a feasibility and preliminary efficacy non-randomized study of an evidence-based one-session pain relief skills class (Empowered Relief) delivered online to a single national class cohort of people with Marfan and related diseases. Adults living in the United States with chronic pain and a self-reported diagnosis of Marfan and related diseases were recruited via The Marfan Foundation. Data were collected at baseline; immediately post-treatment; and at follow-up months 1, 2, and 3. Mixed effects model for repeated measurements (MMRM) regression modeling was used to estimate the average symptom change from baseline. We enrolled 114 participants of which 92(80.7%) attended the online treatment class at once. For N=92: sample mean age was 48 years (SD=15); 69(75%) were female; 78(85%) were European-American/White; 62(67%) with an annual household income >$50,000; 5.5(SD=1.6) average pain intensity; 64.7(SD=5.3) average PROMIS pain interference; 55.4(SD=9.8) average PROMIS depression. For feasibility, treatment attendance 92(80.7%) exceeded our threshold of 70%. Average treatment appraisal ratings for all seven items met our threshold of 4.8(80%). For preliminary efficacy, at 3 months, pain intensity and pain interference (primary outcomes) were significantly improved as well as all secondary outcomes (all p-values <0.001). Limitations include a non-randomized design and an 85% White sample. Multidimensional and clinically meaningful symptom reduction at 3 months justifies a future randomized trial. Results suggests an avenue for accessible behavioral pain care for people with Marfan and other rare disease.

Rural-Urban Differences in Non-Drug Therapy Use for Pain Among US Military Veterans Treated with Long-Term Opioid Therapy for Chronic Pain

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Non-drug therapies (NDTs) are first-line chronic pain treatments. Effects of Prescription Opioid Changes in Veterans (EPOCH), a nationally representative prospective longitudinal cohort study, annually surveyed US Veterans Affairs (VA) patients treated with long-term opioid therapy for

chronic pain. This analysis compared rural and urban participants' meaningful use of NDTs for pain at baseline (2016) and evaluated rural and urban NDT use trends through early 2020. Among EPOCH survey participants (baseline N=9,248), 45% (4,120) resided in rural areas and 55% (5,128) resided in urban areas. Participants reported behavioral (psychotherapy, relaxation, meditation), exercise (stretching/strengthening, aerobic, yoga, and tai chi), and manual (acupuncture, chiropractic, and massage) NDT use. Investigator/clinician consensus defined cutoffs for meaningful use. Descriptive statistics and generalized estimating equations models compared meaningful NDT use between rural and urban residents, adjusting for age, sex, race, and ethnicity. Meaningful behavioral therapy use was less common among rural residents (33%) than urban residents (37%; RR=0.88, 95%CI 0.83-0.95), particularly psychotherapy. Meaningful exercise therapy use was less common among rural (36%) than urban residents (40%; RR=0.92, 95%CI 0.85-0.99), particularly stretching/strengthening and yoga. Meaningful manual therapy use was less common among rural (31%) than urban residents (35%; RR=0.88, 95%CI 0.82-0.95), particularly acupuncture. Rural-urban differences in meaningful NDT use persisted in longitudinal models, and trends within rural and urban subgroups fluctuated similarly over time. Overall, meaningful NDT use for pain was less common among rural residents than urban residents within a nationally representative cohort of US military veterans treated with long-term opioid therapy for chronic pain.

Integrating Two Non-Pharmacologic Pain Management Strategies For Musculoskeletal Pain In Primary Care Settings

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The Centers for Disease Control and Prevention (CDC) Clinical Practice Guideline for Prescribing Opioids for Pain advocates for non-pharmacological treatment for chronic pain. However, the adoption, documentation, and implementation of these guidelines in clinical practice are hindered by gaps in primary care clinic resources and workflows. Two effective non-pharmacological approaches for managing chronic pain are exercise and transcutaneous electrical nerve stimulation (TENS), both of which have also been shown to reduce opioid usage. Here, we present the results of implementing the Bundle for Exercises and TENS (BEsT). This model was designed to facilitate the prescription of exercise and TENS as part of an individualized care plan. Our primary objective was to assess the effectiveness of BEsT in treating patients with chronic musculoskeletal pain in three primary care clinics. Control charts were developed to track provider behaviors in prescribing opioids, non-opioid analgesics, TENS, exercise, and physical/occupational therapy (PT/OT) referrals. Surveys capturing provider perceptions were conducted, along with summative focus groups. Control charts revealed statistically significant changes in the prescription rates of TENS, exercise, and opioids in two out of three clinics. The maximum prescription rate for TENS increased from 4% to 20%, and for exercise from 0% to 13% during the training period. Across all clinics, opioid prescriptions decreased from 26% to 14%. Providers identified several key advantages of BEsT, including the auto-populate feature, the availability of patient education materials, and the reduction in opioid use. However, they also noted disadvantages, such as increased time and staff burdens and workflow disruptions.

Human Spinal Meninges Express Markers of Innervation which may be Altered in Individuals with Low Back Pain

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While cranial meninges are widely implicated in the pathophysiology of migraine, little attention has been given to a possible role of spinal meninges in low back pain. Rodent literature suggests a lack of nociceptor innervation of spinal dural meninges; however, it is unclear if this is true in humans. We explored human spinal meningeal innervation while looking for differences in individuals with low back pain. Bulk RNA sequencing was performed on spinal meningeal samples from organ donors with (n=5), or without (n=31) a history of low back pain. Bulk RNA sequencing data was analyzed using DeSeq2 and differentially expressed genes (DEGs) were calculated (log2fold change >0.585, adjusted p-value <0.05). Spinal meninges were sectioned and stained for glial fibrillary acidic protein (GFAP), peripherin, tryptophan hydroxylase (TH), and CD31. RNA sequencing revealed several markers suggestive of nociceptor innervation including SCN9A, TRPV1, and CALCA. We found 179 DEGs between those with and without low back pain, with 120 being upregulated. Upregulated genes revealed enrichment of biological processes including myelination, neuron projection, and neurogenesis. Further, several upregulated genes suggested increased presence and activity of Schwann cells including GFAP, MPZ, and PMP2. Staining of spinal meninges revealed the presence of Schwann cells (GFAP), neurons (peripherin, TH), and vasculature (CD31). Our results suggest a possible nociceptor or sympathetic neuron innervation of spinal meninges, or both, that may be altered in individuals with low back pain. Future work will need to follow up on the potential involvement of spinal meninges in the pathophysiology of low back pain.

Opioid Use May Enhance the Analgesic and Antidepressant Response to Ketamine: Preliminary Findings from a Small Observational Study

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Pain and mood are influenced by the endogenous opioid system and its interactions with exogenous ligands. Ketamine has received attention for treating pain and mood disorders, and its mechanism of action has largely been attributed to N-methyl-D-aspartate (NMDA) receptor antagonism. Emerging research suggests that ketamine also functions as a positive allosteric modulator of the mu-opioid receptor (MOR), enhancing responsiveness to opioids with minimal direct activation of the MOR (Gomes et al., 2024). Leveraging real-world clinical care data, we explored how opioid use influences the analgesic and antidepressant response to ketamine. In an ongoing observational study, 34 patients receiving a 5-to-7-day inpatient ketamine infusion for chronic pain completed self-rated measures of pain intensity and depression at baseline and at intervals up to 12 months post-infusion. We limited our analysis to the first 4 months post-infusion, as most patients received additional ketamine infusions during this period and discontinued self-reported measures afterward. Using mixed-effects models, we observed that baseline self-reported opioid use was associated with a 1.3-point greater reduction in pain

intensity scores (95% CI -0.7 to 3.3) on the 0-10 numeric rating scale and a 9.7 percentage point greater improvement (95% CI -1.6 to 21.0) in the percent change of PROMIS Depression scores. In summary, opioid use may enhance the analgesic and antidepressant response to ketamine in patients with chronic pain. This exploratory analysis provides hypothesis-generating insights into how ketamine's positive allosteric modulation of the MOR may affect therapeutic outcomes for specific subgroups of patients with chronic pain.

Robust Peritraumatic Immune System Activation Improves Pain Recovery Following Traumatic Stress Exposure

Brittanie Winfield, Samuel McLean, Matthew Mauck, Ying Zhao, Sarah Linnstaedt; University of North Carolina - Chapel Hill

Traumatic stress exposures (TSE) are common. While most individuals recover following TSE, a substantial subset develop chronic musculoskeletal pain (CMP), a morbid and costly condition with few interventions to prevent/reduce it. Understanding the molecular mechanisms driving CMP could identify therapeutic targets. In this study, we assessed whether neutrophil-driven innate immune mechanisms shown to facilitate the resolution of acute low back pain (Parisien, 2022) are also important to CMP resolution following TSE. We used available pain and blood RNA data from the AURORA study, a longitudinal emergency department (ED)-based study of TSE survivors, to assess differential gene expression across the ED and 6-month timepoints (n=404 samples, paired). Differentially expressed genes (DEGs) were assessed via DESeq2 in each of four pain trajectory groups (Beaudoin, 2023). No DEGs were identified for the pain trajectory with high unremitting pain. In contrast, we identified >3,500 DEGs (FDR $p<0.01$) for the pain recovery group (high acute pain in the ED that resolved by 6 months). Pathway enrichment analyses via fgsea identified neutrophil degranulation and innate immune activation as important to recovery. Further, RNA expression-estimated immune cell-type analyses showed that neutrophils were elevated early after TSE but decreased by 6 months in those with a CMP-recovery phenotype ($t=3.81$ $p=0.001$). Finally, we found that individuals with poor recovery had lower cortisol levels at the time of TSE, suggesting a blunted stress-immune response in those who develop CMP. Additional studies are needed to further validate and extend these results and to identify specific therapeutic approaches that encourage recovery.

Examining Patient Engagement Attributes and Proximal Outcomes in Opioid-Treated Chronic Low Back Pain: A 3-Month Study

Fatih Kunkul, Aleksandra E. Zgieska, Roger L. Brown, Linda D. Oakley; University of Florida

Management of chronic low back pain (CLBP) requires active patient role in their care. Patient engagement that includes active involvement in health care decisions and proactive self-management strategies has been shown to be associated with treatment outcomes. This study examines the antecedents, attributes, and consequences of patient engagement in individuals with opioid-treated CLBP. Data from 770 participants in a randomized controlled trial were analyzed. Patient engagement was operationalized through session attendance, home practice adherence, and self-reported involvement in care. Antecedents (e.g., pain catastrophizing and treatment expectation), attributes (e.g., pain acceptance, treatment expectation), and consequences (e.g.,

quality of life [QoL] and treatment satisfaction) of engagement were explored using descriptive and mediator analyses. Higher patient engagement was significantly associated with improved mental and physical quality of life (QoL; $p<0.05$). Key antecedents of engagement included lower levels of pain catastrophizing, higher treatment expectations, and greater baseline pain acceptance (all; $p<0.05$). In mediation analyses, pain acceptance emerged as a significant pathway linking pain catastrophizing to mental and physical QoL ($p=0.0034$ and $p=0.0109$, respectively). Treatment expectations also significantly mediated the relationship between pain catastrophizing and QoL outcomes, particularly for mental QoL ($p=0.0073$) and physical QoL ($p=0.0167$). Patient engagement in CLBP management can be described as the complex interaction of psychological, behavioral, and contextual factors. Our findings show the potential influence of pain acceptance, on treatment outcomes including treatment expectations, and patient engagement behaviors in improving QoL. Future research should explore mechanisms linking patient engagement to long-term outcomes, including the interplay of psychological and contextual factors. The research reported in this abstract was funded through a Patient-Centered Outcomes Research Institute (PCORI) Award (OPD-1601-33860). ClinicalTrials.gov#: NCT03115359.

Epigenome-Wide Association Study Identifies DNA Methylation Loci That Predict Chronic Musculoskeletal Pain Outcomes After Traumatic Stress Exposure

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Millions of people present to US emergency departments (EDs) after traumatic stress exposure (TSE). While most recover, a substantial subset develop chronic posttraumatic musculoskeletal pain (CPMP). In this study we performed an epigenome-wide association study (EWAS) to examine potential epigenetic predictors of CPMP development. Data from a longitudinal observational study of trauma survivors (the AURORA cohort) and data compiled from four other ED-based cohort studies (the “ITR” cohort), served as our discovery (n=705) and validation (n=289) cohorts. Methylation levels in DNA isolated from blood collected within 72 hours of TSE were measured using the Illumina MethylationEPIC array. The relationship between peritraumatic methylation levels and CPMP over time (8-week, 3-month, 6-month pain levels) was first assessed across all CpGs in the AURORA cohort. CpG sites that met a pre-defined statistical significance threshold were then assessed for validation in the ITR cohort. Methylation levels at validated CpGs were correlated with mRNA expression. In the discovery EWAS, no CpG sites met a strict false discovery rate threshold (FDR p<0.05). However, n=174 CpGs met a commonly reported suggestive threshold (p<1×10 -4), including enrichment of CpGs in axon guidance-related genes (ABLIM3, DCC, PIK3R3, ROBO1, SEMA6D). Of note, cg03484678 and cg04590170 in DCC and LMO2 replicated in the validation cohort. Methylation levels across many CpG sites correlated with mRNA expression levels. These data suggest that DNA methylation levels in potentially pain-relevant genes predict CPMP development. Future studies should further validate these findings and assess mechanisms through which epigenetic changes in the identified genes contribute to CPMP pathogenesis.

Pain and Heart Rate Variability In Caregivers Of People With Dementia And Non-Caregivers

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It is estimated that around 50% of caregivers experience chronic pain and caregiver burden and at least a quarter experience pain that limits daily activities. Heart rate variability has been utilized as an objective measure of stress and caregiver burden. While most research to date has focused on negative aspects of living with dementia, little research has investigated differences in pain and heart rate variability in caregivers as compared to non-caregivers. Weekly online reports of pain intensity and pain interference were collected on visual analog scales and heart rate variability total scores were collected nightly via Emfit bed mats for three months in the Oregon Center for Aging & Technology (ORCATECH), a study using unobtrusive remote home sensing and monitoring of health metrics in older adults. The sample consisted of older adult twelve caregivers and twelve non-caregivers matched on age, education, and bed-sharing habits. Mean age was 73.7 ± 6.3 years, mean education was 15.4 ± 2.4 years, and 75% were female. Over three months, non-caregivers showed higher (better) heart rate variability scores than caregivers (61.7 versus 49.7, respectively, p=0.16). Neither pain intensity (caregivers = 2.1; controls = 1.5; p=0.78) nor pain interference (caregivers = 1.7; controls = 1.6; p=0.71) differed between groups. While this study was not powered to identify meaningful differences, it demonstrates the feasibility of using an objective digital assessment of caregiver burden (heart rate variability) in relation to caregiver pain. The findings could facilitate greater understanding of the role pain plays in caregiver burden.

The Complex Link between Childhood Trauma, Chronic Stress and Chronic Pain: Challenges in Multimodal Research

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While chronic pain consists of a complex interplay of biopsychosocial factors influencing pain experiences, multimodal research can prove challenging to corroborate (Craner et. al, 2022). Childhood traumatic events and chronic stress levels both contribute to hypothalamic-pituitary adrenal (HPA) axis abnormalities and are significantly associated with psychosocial functioning and pain related outcomes (Quidé et al. 2020). The current study utilizes a multi-modal approach to primarily investigate the relationship between self-reported childhood traumatic burden impacting hair stress hormone concentration and subsequent pain intensity in participants with chronic postsurgical pain (CPSP). Participants included 30 people with CPSP (pain persisting 3 months after surgery) and 24 controls without chronic pain or a surgical history. Chronic cortisol levels over the past 3 months were assessed by hair cortisol analysis while trauma burden scores were reported using the Childhood Traumatic Events Scale (CTES). Pain intensity was self-reported using the numeric rating system. Results of a Pearson's correlation revealed significant negative association between trauma burden and baseline pain ($r = -0.400$, $p = 0.29$) in the CPSP patients and no significant relationship in health controls ($r=0.258$, $p = 0.235$). The observed lack of significant associations highlights the inherent complexity of linking biological and

psychosocial measures in multimodal research, underscoring the need for methodological advancements in integrating such diverse datasets. Future research could explore longitudinal designs to better capture dynamic changes in trauma, stress, and pain over time and include additional biomarkers of HPA axis function. Funded by National Institutes of Health (R35GM142676-01).

Human Molecular Mechanisms of Lumbar disc degeneration: A Scoping Review
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Lumbar disc degeneration (LDD) is associated with chronic low back pain. A structured synthesis on the mechanisms of human LDD is lacking. This scoping review summarizes the current knowledge of molecular mechanisms associated with human LDD, and identifies knowledge gaps to be addressed by future research. A systematic search of 12 databases identified 8,298 relevant studies. We included studies analyzing human lumbar degenerative disc tissues from adult patients with radiologically diagnosed LDD, excluding those with sample sizes below 20, degenerative disc tissues from organ donors or non-lumbar spinal segments, and findings based solely on animal data or public repositories (e.g., Gene Expression Omnibus) without clinical validation. A total of 159 studies were identified for data extraction, with 25 selected for final synthesis after further evaluation. Current evidence converges to inflammatory cytokines and signaling pathways (e.g., TNF-α, NF-κB), cellular senescence resulted from oxidative and mechanical stress (e.g., p300, Piezo1, ferroportin), extracellular matrix (ECM) degrading enzymes (e.g., MMP14, ADAMTS-7), and dysregulated lipid metabolisms (e.g., oxidized low-density lipoprotein/LOX-1, LPCAT1-PC). Other regulators, such as SIRT1 and IGFBP5, are implicated in cartilage repair and mesenchymal stem cell (MSC) survival, while non-coding RNAs, including microRNAs and circular RNAs, are involved in apoptosis, ECM remodeling, and immune modulation. Major weaknesses in the literature include limited sample sizes, lack of comprehensive phenotypic profiling and stratification, and reliance on in vitro or animal experimental data. Future research should prioritize the use of multi-omics and bioinformatics analyses, integrating molecular, imaging, and clinical data to identify relevant mechanisms for LDD.

Assessing the Efficiency of Conditioned Pain Modulation Using Contactless Laser Stimulation: A Reliability and Evoked Potential Study in Healthy Individuals
Xiaohan Zhang, Patrick Realyvasquez, Whitney Carter, Maya Shah, Mohapatra Sejal, Aryan Mhaskar, Julie Wang, Hoang Le, Shuqi Ye, Dan Wang, Shayan Moosa, Patrick Finan, W. Jeff Elias, Jeff C. Liu; University of Virginia School of Medicine

A reliable protocol for assessing the efficiency of conditioned pain modulation is crucial for developing objective biomarkers of pain modulation profiles. This study examines the reliability of contactless cutaneous laser stimulation for assessing conditioned pain modulation and explores whether laser-evoked potentials (LEPs) can serve as biomarkers of pain modulation profiles in healthy individuals. Twenty-seven healthy participants (14 females; mean age: 24.6 ± 11.3 years) completed two CPM study sessions spaced one to two weeks apart. Conditioned pain

modulation (CPM) was assessed using ice water immersion as the conditioning stimulus and 30 triplet laser stimuli (designed to elicit 50/100 pain intensity) as the test stimulus. Pain intensity for each test stimulus was rated on a visual analog scale (VAS) ranging from 0 (no pain) to 100 (maximum pain), with 50 indicating moderate pain. CPM efficiency was calculated as (S1_Pre - S1_Post)/ S1_Pre) x 100%. CPM results were consistent across two visits (CPM: 40.6 ± 26.6% and 36.4 ± 25.0% for visits 1 and 2; $p < 0.05$, one-sample Wilcoxon rank-sum test). Relative test-retest reliability examined by intraclass correlation (ICC) indicated that ICC3,1 was 0.61 ($p = 0.0003$). Significant correlations between CPM efficiency and LEP_N2P2 attenuation were observed in the C3 and C4 sensorimotor channels ($p<0.01p<0.01$, Spearman's rho test). Conditioned pain modulation assessed using contactless cutaneous laser stimulation shows reliable results over a 1-2 week interval in healthy individuals. Laser-evoked potentials may serve as a valuable objective biomarker for determining pain modulation profiles.

Increasing Enrollment of Rural Residents in a Pragmatic Clinical Trial Conducted in Outpatient Physical Therapy Clinics

Jonah Pedelty, Kari Vance, Dana L. Dailey, Heather Reisinger, Carol GT Vance, Ruth Chimenti, Andrew Post, Elizabeth Johnson, Michele Costigan, Maxine Koepp, Trevis Huff, Barbara Van Gorp, Dixie Ecklund, Emine O. Bayman, Bridget Zimmerman, Kristin R. Archer, Leslie J. Crofford, Kathleen Sluka; University of Iowa

The purpose of this study was to review community engagement efforts aimed at increasing participation in the pragmatic clinical trial Fibromyalgia TENS in Physical Therapy Study (FM-TIPS). FM-TIPS was implemented in 25 outpatient physical therapy clinics across seven states to examine if TENS in addition to physical therapy improves movement-evoked pain. We divided the clinics into three groups: Targeted Rural (TR), Targeted Low Enrollment (TLE), or Non-Targeted (NT). The community engagement (CE) strategies were developed in collaboration with local clinicians and were multifaceted, individually tailored to each community, and aimed at increasing enrollment at TR and TLE clinics. Strategies included putting up flyers, social media posts, mailing postcards, community events or provider letters. Before community engagement strategies (Pre-CE) were implemented, TR and TLE clinics screened a combined average of 10 patients per month and enrolled an average of 3.9 participants per month, for a screen to enrollment rate of 2.6:1. Post-CE, TR and TLE clinics screened an average of 13.7 patients per month and enrolled an average of 7.5 participants per month, for a screen to enrollment rate of 1.8:1. The screen to enrollment ratio at NT clinics slightly decreased from 2.1:1 Pre-CE to 1.9:1 Post-CE. These data suggest that community engagement efforts led by the study team increased enrollment without increasing clinician burden by substantially reducing the screen to enrollment ratio at TR and TLE clinics. Funding source: NIH Grant UG3/UH3 AR076387 Supplment S2.

A Multimodal Investigation of Temporal Summation of Pain in Healthy Controls

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Temporal Summation of Pain (TSP) phenomena can be evoked using various stimulation

modalities, but differences between them remain unexplored. This study compares TSP across different modalities in healthy controls. Twenty-five healthy controls (15 females; mean age 23 ± 8.4 years) participated in the present study. Each subject underwent TSP assessments using five stimulation modalities, including contactless heat (cutaneous laser, 30 triplets (ISI: 1.5 s), baseline pain intensity (BPI): 50/100), mechanical pressure (pressure algometry, 20 trials, 1Hz, baseline intensity: 60/100), punctate mechanical (Von Frey filament, 128/256Nm, 10 trials, 1Hz, BPI: 60/100)), and contact heat applied in tonic (2 trials (right and left forearm), 20s, BPI: 60/100) or phasic modes (20 trials, 1Hz, BPI: 60/100). Participants reported pain intensity using a visual analog scale (VAS) ranging from 0 (no pain at all) to 100 (maximum pain imaginable), with 50 indicating moderate pain. A significant proportion of the subjects showed TSP when assessed with cutaneous laser, mechanical pressure, punctate mechanical stimuli but not with contact heat ($p < 0.05$, One sample proportion test). TSP showed significant differences across the five stimulation modalities ($p < 0.05$, One-way ANOVA). Greater TSP was observed for cutaneous laser (27.82 ± 4.32; (mean ± std)), mechanical pressure (17.75 ± 4.14), punctate mechanical (16.64 ± 3.85), while both contact heat with phasic (0.90 ± 0.68) or tonic mode (0.07 ± 0.07) evoked minimum TSP. TSP assessment results vary significantly by modality, highlighting the need to consider modality differences in future TSP research.

Outcomes Associated with Participation in a Whole Health Interdisciplinary Team Program for Chronic Pain: A Retrospective Chart Review Study

Jody Caretti, Stephanie Smith, Jennifer Naylor, Beth Darnall, Anne Black, Samantha Harden, Rena Courtney; PREVAIL Center for Chronic Pain

Chronic pain disproportionately impacts U.S. military Veterans and is most effectively managed by a pain interdisciplinary team (IDT). The PREVAIL (not an acronym) IDT clinical program at the Salem VA Health Care System in Central Appalachia integrates the VHA Whole Health System and emphasizes active self-management strategies for chronic pain. PREVAIL IDT consists of an initial evaluation with 5 specialty pain providers, monthly coaching calls, and a 6-month follow up visit with the IDT. To determine the preliminary efficacy of the program a retrospective chart review study was performed including Veterans who participated in the program during the first 2 years of operation (N= 374). Paired sample t-tests compared baseline and 6-month data within person for the PEG, PROMIS-29, and UW-CAPS-6.Results from those who completed clinical follow-up surveys (PEG= 200, PROMIS-29 N=183, UW-CAPS-6 N= 112) showed significant improvements in pain severity and interference (PEG Average, $p <.001$; PROMIS-29 Pain Intensity, $p=.002$; PROMIS-29 Pain Interference, $p=.001$), pain catastrophizing (UW-CAPS-6, $p=.017$), sleep disturbance (PROMIS-4, $p<.0001$), physical functioning (PROMIS-4, $p=.003$), and social roles (PROMIS-4, $p=.017$). Anxiety, depression, and fatigue (PROMIS-29) were non-significant.These early promising results show preliminary efficacy of the PREVAIL IDT Track clinical program in reducing key pain outcomes in those who completed the program and completed outcome measures. Future studies using randomized clinical trial methodologies are warranted.

Initial Validity Testing Of A Tool To Identify Risk for Unidentified Pain

Jeffrey Boon, Michelle Failla, Alison Anderson, Bernadette Melnyk, Stephen Bruehl, Ulrike

Muench, Michael Carter, Todd Monroe; The Ohio State University

Unidentified pain, a newly recognized concept, can delay intervention and lead to adverse outcomes. A tool has been developed to assess the risk of unidentified pain for use across populations. The aim of this tool is to help clinicians identify patients in need of further assessment for unidentified pain. It consists of 12 components representing three risk hazards (communication or cognition problems, pain history or causative pain diagnosis, being alone or without proxy report available). Subject matter experts (SMEs) in pain management and non-expert nurse practitioner students evaluated the tool. SMEs were recruited via the American Society for Pain Management Nursing, and non-experts through a nurse practitioner student email list. Participants rated each item on a Qualtrics-administered survey for: (a) relevance to the risk of unidentified pain (content validity) and (b) clarity of wording (face validity). Descriptive statistics and Chi-square analysis compared responses between groups. Relevance ratings ranged from 76.7%-97.4% overall (N=43), 70.0%-94.1% for SMEs (n=20), and 82.6%-100.0% for non-experts (n=23). Clarity ratings ranged from 82.9%-91.9% overall, 70.0%-88.2% for SMEs, and 91.3%-100.0% for non-experts. Significant group differences were noted for clarity on two components. Participants also provided written comments for suggested improvements. Most items were deemed relevant and clear, with only minor clarity issues noted. Future work will refine item wording, provide the complete tool with instructions, and assess feasibility and acceptability of the tool. Further validation studies are recommended to confirm reliability and utility. This study received exempt status from the Institutional Review Board

Transdiagnostic Assessment of Central Sensitization & Psychological Distress

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Central sensitization (CS) is a cross-cutting clinical phenomenon with a neurological basis in which individuals demonstrate or report an amplification of central nervous system-level response to adverse stimuli. While primarily explored in association with physical illness, CS is observed across psychiatric illness, particularly in patients with chronic medical conditions (e.g. fibromyalgia, chronic fatigue, irritable bowel) that can be difficult to treat. It is thought that CS-related physical illness and associated psychological distress mutually maintain one another via overlapping physiological and psychological mechanisms. In the current study, we examined psychophysiological processes relevant to psychiatric symptoms. This is consistent with emerging calls to consider a multi-dimensional approach to psychiatric conceptualization such as NIH's RDoC framework. The importance of sensory processing and sensitivity within a cross-cutting, multi-dimensional framework has been highlighted in recent years as a proposed addition to the RDoC framework. In an outpatient psychiatric sample of 50, participants who reported greater somatic, depressive, or anxiety symptoms also reported greater symptoms of central sensitization on a self-report measure. Participants reporting somatic symptoms also reported higher levels of pain in response to single as well as repeated stimuli during mechanical temporal summation. This is the first known study utilizing psychophysiological pain assessment in a transdiagnostic outpatient mental health clinic to identify associations between psychiatric illness symptoms and CS. We hope that findings will provide a basis for consequent investigations into the relationship between central nervous system processing and psychiatric

symptomatology. Funding: Houston Methodist Foundation - Constance M. and Byron F. Dyer Fellowship Award.

The NIH HEAL Pain Therapeutics Development Program RFA-NS-24-019
Jim Pomonis, Matthew Rice, Mary Ann Pelleymounter; National Institute of Neurological Disorders and Stroke

The HEAL Pain Therapeutics Development Program (PTDP) (RFA-NS-24-019) is part of the Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, a trans-NIH research effort focused on improving prevention and treatment for opioid misuse and addiction and enhancing pain management. The Preclinical and Translational Research in Pain Management is one of six research focus areas across the HEAL Initiative® and is part of a suite of funding opportunities that support the development of safe, effective, and non-addictive small molecule, biologic, and combination product therapeutics to treat pain. Funded investigators work together with the NIH to build a lead development team (LDT) that leverages drug discovery and development expertise to advance their basic research into human testing. The program provides access to senior, ex-biopharma consultants, as well as CRO resources for a variety of activities including medicinal chemistry, manufacturing and formulation, DMPK, GLP toxicology, and Phase I clinical testing. Applications may enter PTDP at the Discovery or Development stage and must include plans through early Phase I testing. Grants are milestone-driven and progress against milestones is evaluated annually for a maximum 5-year grant period. End goals include IND submission, completion of a Phase I clinical trial, and formation of partnerships to progress candidate therapeutics through clinical testing. The HEAL-PTDP has awarded a total of 18 cooperative agreements from academia and small business partners covering a multitude of pain conditions to date. These efforts have resulted in two IND application submissions and product licensing to pharmaceutical companies.

Preoperative Pain Interference as a Mediator of the Relationship between Pain Catastrophizing and Nutrition
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Good nutrition has been linked to less clinical pain, with some studies showing that interventions aimed to improve diet are associated with reduced pain. Understanding links between nutrition and pain may give insight into habits that influence pain persistence and inform preventive nutritional interventions. Pain catastrophizing is a psychological process associated with greater pain interference, but its relationship with nutrition is relatively unexplored. The present cross-sectional analysis is part of an ongoing observational longitudinal study in patients undergoing joint arthroplasty and used assessments collected prior to surgery. We developed a questionnaire to assess patients' nutrition using national recommendations for daily servings of fruit, vegetables, protein, grains, and dairy, along with patients' use of cooking oils and consumption of fried and processed foods. An overall nutrition index score was created for each patient. We investigated relationships between nutrition, pain catastrophizing, and pain interference. Bivariate correlations revealed that lower nutrition was related to both greater pain

catastrophizing and pain interference, which were also themselves significantly related ($p<.05$). Mediation analysis demonstrated that the association between greater pain catastrophizing (IV) and lower nutrition (DV) was mediated by pain interference. An alternative model with nutrition as the IV and pain catastrophizing as the DV also showed a significant mediation by pain interference. These exploratory findings suggest an important relationship between nutrition and the psychological processing of pain. Specifically, pain interference may play an important role in contributing to the relationship between patients' pain catastrophizing and nutrition prior to surgery.

The Impact of Clinical Interaction Styles on Pain Catastrophizing and Neural Processing in Chronic Pain: Insights from fMRI Hyperscanning

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Pain catastrophizing can amplify pain perception in chronic pain patients, leading to greater functional impairment in their daily lives. The therapeutic relationship between patient and clinician plays a crucial role in shaping treatment experiences and influencing clinical outcomes such as pain catastrophizing. This study examined the effects of clinician interaction styles - Augmented (warm/attentive) vs. Limited (neutral/business-like) - for 32 women with fibromyalgia (FM, mean age=38.5±12.7 years). FM participants were randomly assigned to either an Augmented (N=17) or Limited (N=15) dyadic interaction style (trained acupuncturists). Before and after a 3-week acupuncture intervention (6 sessions), fMRI hyperscanning was conducted, involving simultaneous scanning, including real-time video connection and an evoked cuff pressure pain/treatment paradigm. Questionnaires assessed patients' experiences, such as the quality of the therapeutic relationship and changes in pain catastrophizing. Patients rated therapeutic alliance, clinicians' warmth, competence, and level of trust significantly higher in the Augmented group ($t_{alliance}(30)=5.87$, $p<0.001$; $t_{warmth}(30)=6.27$; $t_{comp}(30)=3.09$, $p=0.004$; $p<0.001$; $t_{trust}(30)=6.15$, $p<0.001$). While both groups experienced immediate clinical pain relief after treatments ($p < 0.001$), only the Augmented group reported a significant reduction in pain catastrophizing (TIMExGROUP interaction, $F(1,30)=9.37$, $p=0.005$; Augmented delta=-6.00, Limited delta=0.20). Brain imaging brain-to-brain concordance analyses focused on the social mirroring circuitry, including the temporo-parietal junction (TPJ), to understand the neural mechanisms underlying inter-dyad differences in the quality of the therapeutic alliance. This study underscores the critical role of interaction quality in clinical therapies, highlighting its impact on clinical outcomes, such as pain catastrophizing, and the neural processing of nociceptive signaling.

Anterior Midcingulate Cortex Activity During Pain Catastrophizing Predicts Symptom Improvements Following Cognitive Behavioral Therapy in Fibromyalgia

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Fibromyalgia, a nociplastic pain disorder, manifests as widespread pain, cognitive impairments, and psychosocial distress. Nonpharmacologic treatment approaches, such as cognitive behavioral therapy (CBT), aim to address psychosocial factors and have been shown to produce symptom improvement. This longitudinal randomized controlled neuroimaging trial explored the temporal dynamics in clinical outcomes and fMRI brain activity during CBT in fibromyalgia patients. Symptom improvement was observed consistently during both early (weeks 1–4) and late (weeks 5–8) phases of an 8-week CBT program, though the timing of treatment responses varied among individuals. Baseline brain activity in the anterior mid-cingulate cortex (aMCC) during a pain catastrophizing task emerged as a significant predictor of treatment outcomes. Greater baseline aMCC activation (during catastrophizing) predicted enhanced improvement in pain interference (assessed via the Brief Pain Inventory) for the early phase of treatment ($r=-0.50$), whereas lower aMCC activation predicted greater improvement for the late phase ($r=0.37$). The early and late changes in aMCC activity (during catastrophizing) were correlated with early ($r=0.32$) and late changes ($r=0.38$) in pain interference, respectively. Notably, the predictive accuracy of this neuroimaging metric was comparable to, and sometimes exceeded, that of baseline psychosocial and clinical measures. These findings suggest that neuroimaging metrics could complement traditional psychosocial assessments to refine therapy expectations and optimize treatment strategies for fibromyalgia, pending further validation.
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Investigating the Influence of Gender-Affirming Hormone Therapy on Immune Processing in Cisgender and Transgender Individuals

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There are established gender differences in the susceptibility to chronic pain and associated conditions, with women often showing the highest burden. In mice, the cells responsible for the maintenance of chronic pain appear to be dependent on sex hormone levels, with males utilizing microglia and females utilizing T cells. This difference is thought to be due to testosterone's suppression of T cell activity and estrogen's promotion of T cell activation, potentially the underlying mechanism for the increased susceptibility in women. However, little is known how additional hormones, such as those associated with gender-affirming hormone therapy (GAHT), may shift the balance of immune cells in humans. The present study enrolled pain-free cisgender and transgender men and women to assess immune cell populations, immune cell reactivity, and gonadal hormone levels using flow cytometry and assays, respectively. Preliminary data analyses suggest that those with lower levels of testosterone (transgender women on GAHT and cisgender women) have higher frequencies of CD3, CD4+, and CD8+ T cells. In contrast, those with higher levels of testosterone (transgender men on GAHT and cisgender men) have lower frequencies of CD3, CD4+, and CD8+ T cells. Furthermore, when the cells were stimulated, preliminary analyses suggested that transgender women (on GAHT) and cisgender women had lower levels of activated Th1 cells, but greater levels of activated Th2 cells than transgender men (on GAHT)

and cisgender men. Together these data suggest that the introduction of exogenous hormones through GAHT may shift immunological pain processing pathways and affect risk for chronic pain.

Exploring Patient-Related Barriers In Pain Management For Cancer Survivors: A Narrative Synthesis

Jonathan Zhu, Peggy Compton, Jie Deng, Connie Ulrich; University of Pennsylvania

Exploring Patient-Related Barriers In Pain Management For Cancer Survivors: A Narrative SynthesisJonathan Zhu; Peggy Compton; Jie Deng; Connie Ulrich; University of Pennsylvania School of NursingLife expectancy among cancer survivors has increased due to novel technologies and treatments, but over 30% of this population experiences chronic pain, inhibiting their holistic well-being and quality of life. Despite the existence of many pharmacological and non-pharmacological pain management therapies, patient-related barriers often prevent cancer survivors from experiencing adequate pain management. In this narrative synthesis, literature from 4 databases (PubMed, CINAHL, Scopus, and Embase) was screened, appraised using JBI Critical Appraisal tools, and synthesized using thematic analysis. The most prevalent types of pain management discussed in the articles were non-opioid analgesics, opioids, physical activity, and alternative modalities. Patient-related barriers to pain management were grouped into general barriers, barriers specific to opioid analgesics, and barriers specific to physical activity. The most significant barriers were negative perceptions toward chronic pain, patient-provider communication, opioid-related stigma, undesirable side effects of opioids, and logistical, cognitive, and symptom-related barriers to physical activity. To address these findings, educational interventions for clinicians and cancer survivors/caregivers should be implemented that focus on the biopsychosocial nature of pain, the opioid addiction process, and effective clinical communication. Physical activity should be promoted through peer support group interventions. Future research areas include identifying the efficacy of novel interventions among cancer survivors, as well as investigating behavioral pain management modalities such as cognitive behavioral therapy.Funding: NIH Individualized Care for At Risk Older Adults (T32NR009356).

Development of an Electronic Prescription Bundle of Non-Pharmacological Strategies for Chronic Musculoskeletal Pain in Primary Care

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Chronic pain is experienced by more than 50 million adults in the U.S. with many experiencing pain on most days or every day (Yong 2022). For those seeking pain management, primary care providers are the most common health care provider contacted. At University of Iowa (UI) Health Care, 30% of patients with chronic musculoskeletal pain are seen by primary care providers. Non-pharmacological strategies are part of the Centers for Disease Control and Prevention (CDC) Guidelines for Prescribing Opioids for Chronic Pain. Two non-pharmacological strategies with strong evidence for effectiveness in the management of chronic

musculoskeletal pain are exercise and transcutaneous electrical nerve stimulations (TENS). To assist UI Healthcare Family Medicine and Internal Medicine outpatient clinic providers to quickly and accurately prescribe exercise and/or TENS for patients with chronic pain, we developed an electronic prescription bundle, called The Bundle for Exercises and TEND (BEsT) as part of the individualized plan of care. Development of this evidence-based prescription bundle was informed by conducting formative focus groups with providers and clinic staff; developing a provider order set, with added prompts in the electronic prescription ordering system; creating electronic, hardcopy, and video patient education materials for TENS and exercise; educating and training provider and clinic staff; and reviewing feedback from provider, staff, and patients. Supported by a grant from the American Pain Society and Pfizer.

In Vivo Profiling Of Diazepam And Gabapentin In Rats In The NIH HEAL Initiative Preclinical Screening Platform for Pain Program

Victoria Brings, Sarah Woller, Shalini Sharma, Christopher Conrad, Dhananjaya Kempegowda, Smriti Iyengar; National Institute of Neurological Disorders and Stroke

The Preclinical Screening Platform for Pain (PSPP) program was developed as part of the National Institutes of Health Helping to End Addiction Longterm Initiative to accelerate the discovery and development of non-opioid, non-addictive pain therapeutics. In collaboration with PsychoGenics, Inc., PSPP evaluated clinically used drugs and negative controls using the PSPP workflow, including diazepam and gabapentin. In vivo studies used male and female Sprague Dawley rats in fully powered groups and included vehicle and positive control groups. Experimenters were blinded to treatment, pre-determined inclusion criteria were applied for each endpoint, and groups were balanced by specific variables. In pharmacokinetics studies, diazepam (3, 10 mg/kg) and gabapentin (60, 100 mg/kg) plasma levels were measured to guide dosing for behavioral assays. The Irwin functional observational battery showed that diazepam (1, 3, 10, 30 mg/kg) and gabapentin (30, 60, 100, 300 mg/kg) produced several neurological side effects, including decreased body position and locomotion. In spite of the neurological side-effects noted, 10, 30, 60, and 100 mg/kg gabapentin demonstrated dose- and time- dependent analgesic activity in both mechanical allodynia and guarding behaviors in the plantar incision model and in the mechanical allodynia and cold-induced allodynia behaviors in the L5/L6 spinal nerve ligation (SNL) model. However, 1, 3, and 10 mg/kg diazepam only showed minimal efficacy on mechanical allodynia behavior in plantar incision. These studies demonstrate the rigorous approach employed to evaluate potential analgesics within PSPP.

Peers Enhancing Engagement for Pain Services: Results of a Pilot Trial

Sara Edmond, Daniel Rogers, Anne Klee, William Becker; VA Connecticut Healthcare System

Peer specialists are individuals with lived experience, who work with individuals that are harder to engage in services or need more support to promote self-management strategies. Peer specialists may be a key component to effectively treating chronic pain, but there is limited research in this area. Peer specialists may be well-positioned to use approaches such as motivational interviewing and sharing their lived experience to promote uptake of evidence-based non-pharmacological pain treatments and self-management strategies, which may in turn

lead to improvements in pain-related function and disability. The goal of our study was to examine the feasibility and acceptability of a peer specialist led intervention for patients with chronic pain; we set a priori benchmarks for feasibility and acceptability. We enrolled 31 patients with high-impact chronic pain being seen by an interdisciplinary pain clinic at a VA Medical Center in New England to receive six sessions of peer support; 18/31 completed follow-up measures. Patients were, on average, 62.5 years old, 74% men, and 68% White, with an average pain intensity/interference score of 6.6/10. Our enrollment rate was 23.6% (31/131) and our retention rate was 58%. Overall, Veterans reported intervention acceptability as indicated by scores on the Client Satisfaction Questionnaire. Ten patients participated in qualitative interviews about their experience with many expressing satisfaction: “[I] was really impressed with him… I got the impression from the beginning that he was there for me. He cared about what was happening." Most feasibility benchmarks were met; additional analyses will examine preliminary effectiveness. Funding: VAI21RX004381.

The Role of Androgens On Experimental Pain Sensitivity: A Systemic Review and Meta-analysis

Elizabeth Wu-Chen, Gourav Banerjee, Elise Requadt, Benjamin Hunter, Thomas J Baranski, Whitney Trotter Ross, Hadas Nahman-Averbuch; Washington University in Saint Louis

The Role Of Androgens On Experimental Pain Sensitivity: A Systemic Review And Meta-analysisElizabeth Wu-Chen, Gourav Banerjee, Elise Requadt, Benjamin Hunter, Thomas J Baranski, Whitney Trotter Ross, Hadas Nahman-Averbuch; Washington University in St. Louis, Department of AnesthesiologyAnimal studies have shown androgens, especially testosterone, have an analgesic effect on nociceptive behavior. However, it is unclear if this effect is present in humans. This systematic review and meta-analysis summarize and synthesize the results on 1) relationships between androgens and experimental pain sensitivity, 2) group differences in androgen or pain levels, and 3) the effect of androgen interventions on experimental pain sensitivity. Thirty-one papers were identified. Most studies examined the impact of testosterone on experimental pain, and only a few studies focused on other androgens, such as dehydroepiandrosterone and dehydroepiandrosterone sulfate. Overall, the current data do not support an effect of androgens on experimental pain sensitivity in adult men and women with or without chronic pain. Additionally, contradicting results were found in intervention studies that increased or decreased testosterone levels. Two meta-analyses of the relationships between testosterone levels and pain ratings of heat stimuli and electrical pain thresholds were performed, and no relationships between testosterone levels and heat or electrical pain were detected. Thus, the role of testosterone on experimental pain sensitivity may be minor. There is a need to examine the impact of other androgens and the interaction between testosterone and other hormones on experimental sensitivity.

Prevalence and Characterization of High-Impact Chronic Low Back Pain in Service Members Receiving Physical Therapy Care within Military Treatment Facilities

Jaclyn Sions, Eric Terkpertey, Charity Patterson, Shawn Farrokhi, Brad Hendershot, Christopher Dearth, Emma Beisheim-Ryan; University of Delaware

Subgrouping low back pain (LBP) based on chronicity and impact aligns with the National Institute of Health Task Force on Research Standards for Chronic LBP (Deyo, 2015). Chronic pain subgrouping, albeit not LBP-specific, has occurred within Veterans (Taub, 2023), but not active-duty Service members. Thus, the objective of this secondary analysis was to determine the prevalence and extent of LBP subgroup differences in active-duty Service members receiving LBP care at military treatment facilities participating in a multisite, pragmatic clinical trial (Farrokhi, 2020). We hypothesized LBP characteristics, disability, psychological risk-stratification, comorbidities, and medications would differ among subgroups. Using baseline evaluation data, patients were classified as chronic or non-chronic LBP based on the Task Force definition (Deyo, 2015). Patients with chronic LBP were further classified as having mild chronic LBP if their 3-item Pain, Enjoyment and General Activity Scale (PEG) score was <12 and bothersome chronic LBP if their score was at least 12 (Taub, 2023). Patients endorsing active-duty restrictions were elevated from bothersome to high-impact chronic LBP. LBP was classified for 1410 patients: 29.9% non-chronic, 15.7% mild chronic, 43.6% bothersome chronic, and 10.7% high-impact chronic. Between-group differences were found for LBP-related disability and risk-stratification patient-reported outcomes; presence of radicular symptoms, depression, fibromyalgia, pain in extremities/other joints, headaches, and stomach pain; as well as the use of paracetamol, antidepressants, and gabapentinoids ($p<.050$). Age-adjusted odds ratios highlight that increasing LBP chronicity and impact is associated with greater medical and psychological complexity in Service members and suggest critical targets for holistic rehabilitation. Funding: W81XWH-18-2-0007.

Initial Findings From An Implementation Study Of A Nurse Care Management Model For Rural Primary Care Patients With Chronic Pain

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Individuals in rural communities experience a high burden of chronic pain and often lack access to non-pharmacologic, evidence-based treatments. Implementing comprehensive programs for pain management that include non-pharmacologic treatments could reduce pain interference and improve function. The purpose of this study is to adapt and implement a nurse care management (NCM) model that includes care coordination, cognitive-behavioral therapy (CBT), and referrals to a remotely delivered EnhanceFitness® (Tele-EF) exercise program for rural primary care patients with chronic pain. In phase 1 of our study, the goal was to make refinements of our intervention for rural communities and culturally adapt the intervention for rural Latine populations. As part of phase 1, we engaged two health systems, one in Northeast Washington State and one in Central North Carolina, to pilot the NCM model. Care managers received training and then provided care coordination, CBT and Tele-EF for 6 months. Among 31 pilot participants, the mean age was 57.2 years (SD=11.9), 65% were female, 74% had an annual household income of less than $49,999, and 87% were not employed. The mean baseline PEG score was 6.8 (SD=1.8). Based on adaptations from our learning in phase 1, we will conduct a randomized controlled trial of the adapted NCM model versus usual care in 408 rural participants with a primary outcome of pain interference in phase 2. This study could have a transformative

effect on chronic pain management in rural areas by expanding access to evidence-based treatments through an innovative NCM model. Funding: NIH HEAL Initiative UG3NR020930.

Deficits In Warmth Detection In Individuals With Haploinsufficiency For RUNX1: A Molecular-Anatomical Approach

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The transcription factor RUNX1 is essential for the development and differentiation of murine C-nociceptors. Human fetal immunofluorescence data suggests parallel early C-nociceptor development in humans. In adults, spatial transcriptomic data point to an enriched RUNX1 expression in TRPV1+ pruri-nociceptors, which are hypothesized to innervate superficial skin. DRG neurons expressing the ion channel TRPV1 have been shown to be essential for the detection of warmth and heat. Individuals with heterozygous loss-of-function germ-line variants of RUNX1 show a significant deficit for contact warmth detection. In order to investigate the potential contribution of nociceptive afferents to this observation, we studied the expression of RUNX1 in relation to other transducers of thermal sensation in human DRG neurons using multiplex in situ hybridization. Our results confirm the preferential expression of RUNX1 in TRPV1+MRGPRD+ “non-peptidergic” pruri-nociceptors. This population furthermore expressed the heat-responsive ion channel gene TRPM3, yet was devoid of gene expression for the warmth receptor TRPM2 or the cool receptor TRPM8. “Peptidergic” TRPV1+NTRK1+ neurons by comparison express lower levels of RUNX1. Murine data suggests these neurons innervate deeper layers of the epidermis. This population expressed a wide variety of thermal transducer genes composed of TRPV1, TRPM3, TRPM2 and partially TRPM8. Skin biopsies obtained from healthy volunteers demonstrate a differential innervation of epidermal layers by TRPV1+ nerve fibers. Taken together, these results suggest a functional role of RUNX1 specifically in TRPV1+ pruri-nociceptors innervating superficial skin. The combined study of transcription factors and effector genes provides insight into transcriptional gene networks relevant to human cutaneous sensation.

DNA Methylation Of The NR3C1 Gene And Its Association With Chronic Pain

Ariana Robinson, Javier Tamargo, Yutao Zhang, Zhiguang Huo, Li Chen, Roger Fillingim, Yenisel Cruz-Almeida; University of Florida

Chronic pain is commonly associated with stress, where pain can be a stressor, and stress can, in turn, exacerbate pain. Emerging evidence has implicated DNA methylation (DNAm) as a potential contributor to chronic high impact pain (i.e., pain that significantly limits daily activities), but its connection to stress-related pathways has not been widely explored. The present study examined DNAm patterns of the glucocorticoid receptor (NR3C1) gene and chronic pain impact in middle-to-older aged adults (45-85 years, n=216) who self-identified as non-Hispanic Black and White with and without knee osteoarthritis (OA). The Graded Chronic Pain Scale (GCPS) was used to classify participants as having no pain (n=31, 29.2%), low-

impact chronic pain (n=110, 50.9%), or high-impact chronic pain (n=75, 70.8%). DNA was extracted from blood samples and analyzed using Infinium Methylation EPIC arrays (>850 CpGs). Differential methylation of cytosine-phosphate-guanine (CpG) sites along the NR3C1 gene were compared between pain-impact groups. Three CpG sites along promoter regions (cg08818984, cg03906910, and cg065241) were hypermethylated in individuals with chronic pain compared to pain-free controls. Additionally, cg1629186 (intron) and cg16535116 (promoter) were hypomethylated in high-impact chronic pain compared to those with low-impact or no pain. Our results may help in understanding the interplay between underlying biopsychosocial factors that contribute to variability in chronic pain impact. Future research is needed to evaluate other epigenetic modifications (i.e., histone modifications, noncoding RNA), explore other genes associated with the hypothalamic-pituitary-adrenal (HPA) axis, and examine how these factors correspond to pain variability. Funding Source: NIA (R01AG067757).

Patient-reported Symptom Measures May Modify the Relationship Between Emotional Function and Pain in Head and Neck Cancer (HNC)

Asif Lakhani, Brian Egleston, Janet Van Cleave; The University of Texas Health Science Center at Houston

A person’s emotional function may influence their pain experience. The role of patient-reported symptom measures in modifying the relationship between emotional function and pain in head and neck cancer (HNC) is understudied. This research explores the effect of the NYU Electronic Patient Visit Assessment (ePVA), a patient-reported measure of 21 symptom categories, on the relationship between the level of pre-treatment emotional function and post-treatment pain in 32 patients undergoing radiation therapy with or without chemotherapy for head and neck cancer (HNC). A secondary analysis of a pilot randomized clinical trial of the ePVA to improve outcomes of patients with head and neck cancer (HNC) was conducted using generalized linear models estimated by Generalized Estimating Equations and the European Organization for Treatment and Research (EORTC) QLQ-C30 subscale of emotional function and pain. Participants in the pilot study were randomized to: 1) the ePVA arm or 2) usual care arm. Patients in the ePVA arm completed symptom questions; their responses were automated to the clinical team at point-of-care, enabling real-time interventions. The participants' mean age was 60, and were primarily male (69%), White (81%), Non-Hispanic (81%). Participants receiving usual care had a significant negative relationship between levels of pre-treatment emotional function and pain 1, 3, and 6 months after treatment (p=.012). Participants in the ePVA arm had no association between pre-treatment emotional function and post-treatment pain (p=.492). These findings suggest that use of patient-reported measures in routine HNC treatment may modify the relationship between emotional function and pain. Funding: Oncology Nursing Foundation.

Emotional Function Predicts Pain Outcomes in Head and Neck Cancer

Asif Lakhani, Janet Van Cleave, Carolina Gutierrez, Brian Egleston; The University of Texas Health Science Center at Houston

Patients with Head and Neck Cancer (HNC) undergoing radiation therapy may experience severe pain unresponsive to opioids and challenges in emotional functioning resulting in high anxiety

and severe depression. Competing theories exist on the association between pain and emotional function. Some theories (James-Lange) posit that pain may influence emotional function, whereas other theories suggest emotional function may influence pain levels. As such, this study investigated the association between emotional function before HNC treatment and pain levels after HNC treatment using extant data from a pilot study testing using NYU Electronic Patient Visit Assessment (ePVA)© for remote patient-reported symptom monitoring during HNC treatment. After informed consent, 31 patients with HNC (69% male, 81% white) undergoing radiation therapy with or without chemotherapy completed the emotional function and pain subscales of European Organization Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) QLQ-C30 pre-treatment and at 4, 12, and 24 weeks post-treatment. Using Generalized Linear Models estimated by Generalized Estimating Equations while controlling for gender and cancer stage, the analysis demonstrated a statistically and clinically significant negative association between pre-treatment emotional function and post-treatment pain levels (-0.433, $p<0.0018$, 95% CI, [-0.705, -0.161]). The study findings indicated that patients with better emotional function before HNC treatment reported lower pain levels post-treatment. Future research may include further investigating the association between emotional function and pain levels through mapping anatomical pathology of emotions and pain using functional MRIs of the brain, before and after HNC treatment. Funding: NCI 1R01CA282149/P30CA006927, CPRIT #RP210042.

Ultra Low Frequency Neuromodulation Induces Subthreshold Modulations in Dorsal Horn Interneurons

Liam Matthews, Nishant Verma, Martyn Jones, James Harris, Scott Lempka; University of Michigan

Ultra-low frequency (ULF) neuromodulation utilizes a novel, charge-balanced, biphasic waveform to achieve action potential conduction block in preclinical models and profound pain relief in chronic pain patients. These patients reported no sensory deficits, as would be expected if ULF currents were inducing complete conduction block in the dorsal columns, which predominantly carry touch and proprioceptive information. This motivates our investigation of potential pain relief mechanisms alternative to complete conduction block. Previous studies demonstrate that subthreshold voltage fluctuations on the order of 2mV can alter spike timing and synaptic efficacy. Therefore, the goal of this work was to utilize a computational modeling approach to investigate ULF-induced subthreshold polarization in the human spinal cord. We used a finite element method model of the human thoracic spine to estimate the extracellular potentials generated by ULF currents via clinical electrodes placed in the epidural space. We coupled these potential fields to multicompartment cable models of tonic-firing interneurons distributed in the superficial dorsal horn to assess the subthreshold membrane polarization induced by ULF neuromodulation. Specifically, with 1mA of ULF current, we found maximum polarization exceeding 2mV on cells located under the cathode. Further, we found that a bipole with 16mm center-to-center spacing induced the strongest polarization when compared to 8mm, 24mm, and 32mm spacings. When subject to excitatory primary afferent synaptic input representing non-noxious brush and noxious pinch stimulation, application of 1mA of ULF current modulated activity during both the anodic and cathodic phases of the ULF waveform. Funding: Presidio Medical, Inc.

The Relationship Between Topical Capsaicin Pain and Dermal IL-6 Expression: The Moderating Effect of Pain Catastrophizing

Emily Rosado, Jenna Wilson, Michael Stark, Angelina Franqueiro, Yuhan Lee, Kristin Schreiber; Harvard Medical School

Pro-inflammatory cytokines, such as IL-6, have been implicated as potential mechanistic contributors to chronic pain syndromes. Capsaicin, the active ingredient in many spicy foods, activates neurons through TrpV receptors, promotes inflammation, and has been used in psychophysical testing. The current study employed a novel dermal microneedle patch to investigate the relationship between capsaicin-induced neurogenic inflammation and associated pain, and whether this relationship was moderated by participants' baseline catastrophic thinking. Healthy volunteers completed the Pain Catastrophizing Scale at baseline, underwent Quantitative Sensory Testing (QST), and reported pain severity associated with the application of topical capsaicin to the forearm. Swellable microneedle (MN) patches were applied to sample extracellular fluid from the dermis in both control (untreated) and capsaicin-treated areas. Fluid extracted from MN patches were assayed for IL-6 expression. The amount of intradermal IL-6 was compared between untreated and treated areas, showing a variable difference among participants. Capsaicin-induced pain was significantly associated with the difference in IL-6, such that greater pain severity was related to an increase in IL-6. Greater baseline pain catastrophizing was also associated with an increase in IL-6 expression. Notably, a significant interaction between baseline pain catastrophizing and capsaicin-induced pain was observed, such that pain severity was more strongly associated with IL-6 expression among those with higher levels of pain catastrophizing. These findings suggest that experimentally-induced pain may be associated with discernable alterations in pro-inflammatory responses, and this association may be moderated by an individual's psychological characteristics.

Subjective Memory Problems and Everyday Function in Older Adults with and without Chronic Pain

Tyler Bell, Nathalie Gider, George W. Rebok, Michael Crowe, Karlene Ball, Gail E. Wallace, Sheila Black, Kelsey Thomas, Cynthia Felix, Jeanine Parisi, Caitlin Northcutt; University of California San Diego

Chronic pain is common among older adults and associated with cognitive decline and an increased risk of dementia. Subjective memory problems (SMPs)—self-reported memory difficulties—may serve as early indicators of functional decline preceding dementia, particularly in those with chronic pain. This study examined the associations between SMPs and cognitive, physical, and psychosocial functioning in older adults with and without chronic pain, using data from 1,676 participants in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study. Multilevel models assessed baseline, prospective, and concurrent relationships between SMPs and cognitive performance (memory, reasoning, processing speed), physical function (mobility, grip strength, self-rated function), and psychosocial outcomes (depressive symptoms, social wellbeing), with chronic pain as a moderator. At baseline, higher SMPs were linked to poorer cognitive performance, reduced grip strength, lower self-rated physical function,

and more depressive symptoms, with stronger effects in those with chronic pain. Prospectively, higher baseline SMPs predicted faster declines in memory, reasoning, and physical function, with chronic pain moderating declines in self-rated physical function. Concurrently, increases in SMPs were associated with declines in cognitive and physical performance, but no significant changes in social wellbeing or depressive symptoms. SMPs are more prevalent in individuals with chronic pain and represent markers of functional decline, across cognitive, physical, and psychosocial domains. Multimodal interventions may mitigate the compounded effects of chronic pain and SMPs in older adults, improving quality of life and potentially delaying dementia and disability. Funding: K01AG081559.

Decreased Baroreflex Sensitivity After Surgery is Associated with Elevated Postoperative Pain: A Secondary Analysis

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Baroreflex sensitivity (BRS) influences autonomic regulation and pain modulation. Previous studies report conflicting associations between preoperative BRS and postoperative pain: positive when BRS is assessed pain-free but negative when measured during ongoing pain. This study assessed how postoperative changes in BRS contribute to postoperative pain outcomes and clarified previous conflicting results.Spontaneous cardiovagal BRS and pain (PEG scale) were measured preoperatively and on postoperative days (POD) 1 and 2 in 55 thoracic and cardiac surgery patients. Circulating inflammatory biomarkers (C-reactive protein, albumin, cytokines) were assessed. Statistical analyses included linear regressions and hierarchical models adjusted for demographic, surgical, analgesic, and psychological confounders.Pain scores increased significantly from baseline to POD1 and decreased slightly by POD2, with notable inter-individual variability ($P = 0.0092$). Higher preoperative BRS predicted increased postoperative pain on POD2 ($R^2 = 0.1532$, $P = 0.0031$). A significant interaction between time and preoperative BRS levels ($P = 0.0002$) indicated differing BRS trajectories post-surgery. Patients with higher preoperative BRS experienced larger declines in BRS postoperatively ($R^2 = 0.1243$, $P = 0.0083$). Greater postoperative decreases in BRS were associated with higher postoperative pain ($R^2 = 0.0915$, $P = 0.0248$). These associations remained significant after adjusting for confounders. No significant associations were found between postoperative BRS changes and inflammatory biomarkers (CRP, albumin, cytokines).Our findings help explain discrepancies from earlier studies by demonstrating that postoperative BRS measurements—taken during ongoing pain—are comparable to preoperative BRS assessments conducted under pain, as both are negatively associated with postoperative pain. Conversely, higher pain-free preoperative BRS predicts greater postoperative pain due to larger subsequent declines in BRS after surgery. Funding: NIH R21NS112912.

IGHG4 Expression in C2 Human Dorsal Root Ganglion Potentially Links B Cells to Spreading Chronic Neck Pain

Marisol Mancilla Moreno, Cathryn Payne, Khadijah Mazhar, Asta Arendt-Tranholm, Natalie Yap, Abby Chiu, Michael Wilde, Pooja Patel, Muhammad Saad Yousuf, Diana Tavares Ferreira, Jeffrey Jarvik, Judith Turner, Peter Grace, Christoph Hofstetter, Theodore

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IGHG4 Expression in C2 Human Dorsal Root Ganglion Potentially Links B Cells to Spreading Chronic Neck PainMarisol Mancilla Moreno, Cathryn Payne, Khadijah Mazhar, Asta Arendt-Tranholm, Natalie Yap, Abby P. Chiu, Michael A. Wilde, Pooja J. Patel, Muhammad Saad Yousuf Diana Tavares Ferreira, Jeffrey G. Jarvik, Judith A. Turner, Peter M. Grace, Christoph P. Hofstetter, Theodore J. Price, Michele Curatolo; Center for Advanced Pain Studies, Department of Neuroscience, University of Texas at Dallas, Richardson, TX, USA.Chronic neck pain is a prevalent and burdensome condition with poorly understood molecular mechanisms. Using spatial transcriptomics, we have analyzed the C2 dorsal root ganglia (DRG) of patients with chronic neck pain undergoing atlanto-axial (C1-2) fusion surgery to identify molecular mechanisms underlying human chronic neck pain. One out of 8 patients exhibited very high levels of the immunoglobulin heavy constant gamma 4 gene (IGHG4) in the C2 DRG. IGHG4 encodes immunoglobulin G4 (IgG4), involved in IgG4-related disease (IgG4-RD). This study highlights the novel finding of IGHG4 expression in a human DRG as potential mechanisms of chronic neck pain. Funding: NIH U19NS130608 and 1R01AR078192-01A1.

Adrenergic Receptor-induced Release of miR-133a-3p From Adipocytes Rgulates the Onset of Chronic Primary Pain

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Chronic primary pain conditions (CPPCs), such as fibromyalgia, vestibulodynia, migraine, and temporomandibular disorder affect over 100 million Americans, predominantly women, and pose a significant healthcare challenge. CPPCs arise from genetic and environmental factors that enhance catecholamine tone, potentially through miRNA dysregulation following beta-adrenergic receptor activation. Here, we identify miR-133a-3p as a biomarker of CPPC status and investigate its functions using in vivo and in vitro approaches. Plasma levels of miR-133a-3p are consistently downregulated in humans with >1 CPPC and in rat and mouse models of primary pain. Our data suggest that miR-133a-3p is packaged in extracellular vesicles that are secreted by adipocytes and trafficked to the spinal cord, and that its downregulation is mediated by adrenergic receptors on white adipocytes. In the spinal cord, miR-133a-3p regulates pain-related gene networks, such as the MAPK/ERK pathway critical to sensory neuron activation, particularly in males. Adipose-specific overexpression of miR-133a-3p reverses mechanical sensitivity at plantar, abdominal, and back sites in both sexes in the mouse model of primary pain. These findings implicate miR-133a-3p dysregulation in the pathophysiology of multi-site primary pain across conditions (at least fibromyalgia and vestibulodynia) and species and establish its role in multi-site mechanical sensitivity. The novel role of miR-133a-3p in pain sensitivity highlights its therapeutic potential for millions experiencing primary pain worldwide.

Adults with Symptomatic Joint Hypermobility Report Worse Health-Related Quality of

Life than Adults with Other Chronic Pain Conditions
Emma Estrella, Patricia A. Frazier, Adam T. Hirsh; Indiana University

Chronic pain is prevalent in hypermobile Ehlers-Danlos syndrome (hEDS) and hypermobility spectrum disorders (HSD). We compared individuals with hEDS/HSD to other chronic pain conditions to understand similarities and differences in their pain and health-related quality of life (HRQoL). We recruited U.S. adults via online platforms who self-reported having diagnosed or suspected hEDS or HSD (N=2,125). Participants completed the PROMIS-29 Profile v2.1 (U.S. norms: M=50, SD=10), which assessed pain intensity, pain interference, physical function, fatigue, sleep disturbance, depression, anxiety, and social abilities. Comparison groups included mixed chronic pain conditions (Pope et al., 2021; N=19,546), chronic low back pain (CLBP; Rodriguez et al., 2024; N=1,137), and rheumatic diseases or fibromyalgia (Katz et al., 2017; Ns=240-4,364). Results indicated that hEDS/HSD participants had comparable pain intensity, pain interference, and physical function to the mixed pain group. For all other domains, hEDS/HSD participants had worse scores than all other comparison groups. The most notable differences (medium to large effect sizes) were: 8+ points worse pain interference (vs. CLBP and rheumatic diseases), 7+ points worse fatigue (vs. mixed pain, CLBP, and rheumatic diseases), 6+ points worse depression (vs. rheumatic diseases and fibromyalgia), 7+ points worse anxiety (vs. mixed pain, rheumatic diseases, and fibromyalgia), and 9+ points worse social abilities (vs. CLBP and rheumatic diseases). Despite comparable pain severity, individuals with hEDS/HSD have worse HRQoL than individuals with other chronic pain conditions. These results indicate a pressing need to better understand the pain-related risk and resilience factors among individuals with hEDS/HSD.

Gut Microbiome in Patients with Chronic Low Back Pain Compared to Healthy Controls
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Chronic low back pain (CLBP) is a major cause of disability, lost wages, and health care costs. Gut dysbiosis has been identified as one of the factors that could affect pain. While most studies have been conducted in abdominal pain and fibromyalgia, very limited studies with a focus on the gut microbiome diversity and composition in patients with CLBP. Hence, the purpose of this study was to examine the differences in diversity and abundance of the gut microbiome between patients with CLBP and psycho-behavioral symptoms compared to controls. In a cross-sectional study, men and women (N=30) with CLBP and healthy controls (N=30) were enrolled. Participants completed demographics and psycho-behavioral symptoms (depressive mood, sleep quality, sleep disturbances, physical function, pain interference, and pain severity) assessed using PROMIS measures. Rectal swabs were collected for the gut microbiome, which was processed by 16S rRNA sequencing. Descriptive statistics and standardized pipelines were conducted. Permutational multivariate analysis of variance revealed significant difference in relative abundance of the gut microbiome between A-CLBP and control groups (p=0.03). Compared to controls, patients in CLBP group were older, female, higher BMI, and reported poor physical function, sleep disturbances, and sleep quality. Chi-Square tests yielded significant associations between greater pain interference and depressive mood ($p = 0.004$), sleep disturbance ($p = 0.01$), opioid use ($p = 0.001$), smoking ($p = 0.014$), and BMI ($p = 0.02$). Dietary interventions to

promote healthy gut microbiome as part of a comprehensive pain management program may benefit patients with chronic low back pain.

Frailty Is Associated With Increased Pain In US Veterans With Rheumatoid Arthritis
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Frailty, defined as an increased vulnerability to stressors, is associated with decreased physical function and chronic pain (Lin,2020). [MOU1] [MG2] This relationship is important for older adults diagnosed with rheumatoid arthritis (RA), who tend to report a higher incidence of pain [MG3] and are also more likely to exhibit frailty. The relationship between pain and frailty in RA remains underexplored. Data were analyzed from the Veterans Affairs Rheumatoid Arthritis Frailty and Osteoporosis cohort, which included Veterans aged 335 years old diagnosed with RA. [MG4] Frailty was measured with the Fried Phenotype, and pain was self-reported as part of the Multidimensional Health Assessment Questionnaire (scale of 0-10). Multivariable logistic regression was used to evaluate the association between frailty and pain, controlling for age, sex, race, disease duration, BMI, prednisone, biological and conventional disease-modifying medication use. RA disease activity was included in the multivariable model in a sensitivity analysis.Of the 140 Veterans, the majority were White males, and 15% were classified as frail. Pain levels were higher in the frail group (mean 4.1, SD = 2.4) compared to the non-frail group (mean 5.9, SD = 2.5). Pain was independently associated with frailty (OR = 1.4 [95% CI: 1.1 to 1.7], p=0.004) and was maintained in the sensitivity analysis that included RA disease activity (OR = 1.4 [95% CI: 1.1-1.8], p=0.02). We found a significant association between pain and frailty in a cohort of US Veterans with RA. Future studies will focus on understanding the mechanisms between pain and frailty in RA independent of disease activity.

Optimizing Patient-Reported Outcome Measure Implementation In Spine Care And Pain Management Among Physicians: A Consensus-Based Approach
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Patient-reported outcome measures (PROMs) are vital for assessment in pain care but face implementation challenges. At Spaulding Rehabilitation's spine care and pain management clinics, 50% of physicians report currently integrating PROMs into their practice. However, 25% primarily use PROMs for baseline assessment, presenting opportunities to expand PROMs utilization. This division-wide quality improvement initiative aimed to enhance PROMs implementation by identifying clinically relevant domains and workflow barriers through a needs assessment survey of spine care physicians (n=8) across two clinics. Domain priorities were evaluated using a structured, clinician-informed consensus-building approach, with a pre-specified consensus threshold of ≥70% of physicians rating a domain as ‘Very’ or ‘Extremely Important’. Physicians shared insights on PROMs domain importance, PROMs integration, and implementation considerations. Four domains achieved consensus: pain interference (100%),

physical function (87.5%), spine symptoms (87.5%), and spinal abilities (75%), aligning with recent international consensus on pain outcome measurement. Notably, pain severity fell below consensus threshold (62.5%) despite insurance documentation requirements. Primary physician endorsed implementation challenges included time burden for patients (100%), time constraints during visits (87.5%), and clinical workflow integration (87.5%). 50% of physicians preferred standardized measures and 37.5% favored patient-specific customization. For implementation support preferences, physicians equally favored (62.5%) built-in EHR explanations, simplified measures, and customizable PROMs tailored to patient conditions. The majority of physicians indicated limited confidence in interpreting PROMs. The current findings suggest a hybrid approach supported by system-level solutions and targeted interpretation support may optimize sustainable PROMs adoption and enhance utilization among spine care and pain management physicians.Funding: P2CHD101895.

The Progression of Bodily Distribution of Pain in Patients with Low Back Pain
Elizabeth Leimer, Ridhi Choragudi, Rebecca DeSensi, Maya Maurer, Ajay Wasan, Benedict Alter; University of Pittsburgh Medical Center

Low back pain can have ongoing nociceptive and neuropathic components, both of which are risk factors for the development of nociplastic pain (Fitzcharles, 2021). Nociplastic pain is associated with more widespread pain identified by an increased number of painful regions on a body map (Alter, 2024). This study used patient-reported outcomes (PROs) from an observational cohort from the University of Pittsburgh's Patient Outcomes Repository for Treatment registry to test the hypothesis that the bodily distribution of pain over time changes in patients with low back pain. Included patients had selected at least one low back region as painful on a body map (baseline) and completed a body map at the 3 month follow up visit. Hierarchical clustering was applied to the body maps to assign each to one of nine unique clusters (Alter, 2021). The total number of patients assigned to each cluster at the baseline and 3 month timepoints were compared per cluster and the percent change in cluster membership was determined. The study cohort consisted of 16,546 patients (male n=6,060, female n=10,422, neither selected n=64), mean age (SD) of 58.4 (14.9), and 86.0% racially identified as white. The mean BMI was 31.1 kg/m2 (7.82). A widespread pain cluster, reflecting likely nociplastic pain, had the largest increase in cluster membership between baseline (n=455) and 3 months (n=592, 30.1%). Therefore, in a subset of patients with low back pain, there is evidence of new nociplastic pain developing over three months. Future studies will further investigate these changes.

The NIH HEAL Initiative® Preclinical Screening Platform for Pain
Sarah A. Woller, Victoria E. Brings, Christopher Conrad, Shalini Sharma, Dhananjaya Kempegowda, Smriti Iyengar; National Institute of Neurological Disorders and Stroke

Goal: To advertise an NIH HEAL Initiative® program aimed at accelerating the development of non-opioid, non-addictive pain therapeutics.The Preclinical Screening Platform for Pain (PSPP) program was developed as part of the National Institutes of Health Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, with the goal of accelerating the discovery and

development of non-opioid, non-addictive pain therapeutics. The PSPP program accepts small molecules, biologics, natural products, and devices from industry, academic, or government asset owners worldwide. The preclinical evaluation of submitted assets is performed by a National Institute of Neurological Disorders and Stroke (NINDS) contract facility, PsychoGenics Inc. (PGI), in a blinded and confidential manner at no cost to the PSPP program participants. The PSPP program uses a stepwise approach to evaluate assets and, after each step of evaluation, data are reviewed before an asset is advanced within the program. Initial asset evaluation uses in vitro functional screens to understand whether there is undesirable activity at opioid receptors or known targets associated with risk for abuse liability or safety concerns. Assets can also be evaluated in pharmacokinetic studies and assays to understand potential neurological side effects, then can be assessed for efficacy in pain-related models using two endpoints per model. Finally, assets with demonstrated efficacy can be evaluated for abuse liability in vivo using either intravenous self-administration or conditioned place preference. This presentation will focus on describing this one-stop resource available to the community developing pain therapeutics, including eligibility and how to participate in the PSPP program.

NIH HEAL Initiative Funding Opportunities in Translational Pain Research and Therapeutics Development

Rachel Weinberg, Mary Ann Pelleymounter, Moria Bittmann, Julia Bachman, Karlie Sharma, Smriti Iyengar, Eric Hudak, Emily Caporello; National Institute of Neurological Disorders and Stroke

The National Institutes of Health (NIH) Helping to End Addiction Long-term (HEAL) Initiative is an aggressive, trans-agency effort to speed scientific solutions to stem the national opioid public health crisis. In support of this goal, the HEAL Initiatives offers several translational pain research and therapeutics development programs to develop, optimize, and advance non-addictive pain treatments. This poster will present current HEAL notices of funding opportunities (NOFOs) for translational pain research and therapeutics development programs. These NOFOs include development of small-molecules, biologics, natural products, and devices to treat pain as well as identifying new targets within the druggable proteome and discovery of mechanisms of pain relief by approved medical devices. NOFOs are available to researchers across all career stages in academia, industry including small businesses, government, and medical sectors. Attendees will be informed of programmatic priorities and available funding opportunities in translational pain research so that they can identify the appropriate funding mechanisms and connect with program officials.

The Impact Of Gender On Co-Occurring Chronic Overlapping Pain Conditions And Pharmacotherapy In Veterans With Fibromyalgia

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Fibromyalgia is a chronic widespread pain condition that predominantly impacts women. Persons with Fibromyalgia are at risk for having other chronic overlapping pain conditions

(COPCs) and psychiatric comorbidities. While prior research has focused on gender-differences regarding pain characteristics, psychological symptoms, and coping strategies, less attention has been given to the impact of gender on COPC comorbidity and the risk for receiving multiple central nervous system (CNS)-active medications. The objective of the current study was to determine the prevalence of additional COPCs among men and women Veterans with Fibromyalgia and the impact of gender on the number of CNS-medications (including psychiatric medication), frequency of CNS-medication changes, and number of prescribers. Administrative data from Veterans Affairs (VA) were used to identify VA-served Veterans with Fibromyalgia (N = 30,462), of which 17,939 were female (58.89%) in 2022. COPC diagnoses were assessed using a validated algorithm (Schrepf et al., 2020). A one-year observation period was used for the CNS-medication study outcomes. Women were more likely to have a comorbid COPC, particularly migraine (18% men vs. 34% women). Women were prescribed a greater number of concurrent CNS-medications (IRR: 1.08, 95% CI: 1.06, 1.10), had more CNS-medication changes (IRR: 1.15, 95% CI: 1.13, 1.17), and had more prescribers (IRR: 1.08, 95% CI: 1.06, 1.10). These differences persisted, but were attenuated, after adjustment for demographic and clinical characteristics using negative binomial regression. Women Veterans with Fibromyalgia have an increased likelihood of additional COPCs and experiencing patterns of prescribing that may confer risks related to medication use.

Evaluating Team Composition, Nonpharmacological Referral Patterns, and Pain Outcomes in a Veterans Health Administration Integrative Pain Team: A Quality Assessment/Improvement Project

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The Department of Veterans Affairs (VA) has increasingly promoted non-pharmacologic methods via multidisciplinary integrative pain teams (IPTs). However, research on contemporary IPTs is limited in key areas, including 1) characterizing team composition, 2) evaluating whether IPTs facilitate non-pharmacological treatment, and 3) examining clinical outcomes of IPT-based treatment. Addressing these questions at our site, this quality assessment/improvement project analyzed referral patterns and scores on the PEG pain and Patient Global Impressions of Change scales from 117 patients who completed intake evaluations with the VA San Diego IPT from November 2022 to October 2023. Fifty-seven patients (47.72%) had follow-ups averaging 94 days post-intake (SD = 54.11). First, regarding team composition, IPT evaluations involved specialists in pain medicine, pharmacy, physical therapy (PT), social work, psychology, and whole health management. Next, we examined rates of post-intake referrals to a group-format psychology and PT (i.e., nonpharmacologic) intervention and to individual follow-up with pharmacological and nonpharmacological specialists on the team. Of the 117 patients, 67.52% were referred to pharmacological and nonpharmacological specialists, 18.80% were referred only to nonpharmacological specialists, and 4.27% were referred only to pharmacological specialists. Finally, regarding clinical outcomes, patients with follow-up data (N = 57) showed longitudinal improvements in past-week average pain intensity (estimate [SE] = -0.91 [0.34], p = .01) and interference (estimate [SE] = -1.19 [0.42] p = .01). Most reported that their pain had minimally

(21.05%) or much/very much (52.63%) improved. These results reflect the capacity of our IPT to facilitate non-pharmacological care with observed improvements in pain and functioning.

The Roles Of Pain Catastrophizing And Pain Resilience In The Relationship Between Pain Intensity And Pain Outcomes: A Sequential Mediation Analysis
Melissa Makhoul1, Emily J. Bartley; University of Florida

Chronic musculoskeletal pain (CMP) is highly prevalent and disabling. In Lebanon, its burden is exacerbated by ongoing crises, including the economic collapse, COVID-19 pandemic and Beirut blast. While extensive research has identified pain catastrophizing as a potent predictor of poorer pain outcomes, less is known about how positive psychological factors, such as pain resilience, contribute to optimal pain-related functioning. Additionally, the dynamic interplay between pain intensity, pain catastrophizing, and pain resilience on pain outcomes has not yet been empirically examined. This study aimed to examine the serial mediating effects of pain catastrophizing and pain resilience on the relationship between pain intensity and pain outcomes including pain interference, physical and mental health-related quality of life (HRQoL). A total of 154 Lebanese adults with CMP were recruited from two tertiary medical centers in Beirut. Participants completed self-report measures of pain intensity and interference, pain catastrophizing, pain resilience, and physical and mental HRQoL. Serial mediation analyses using Hayes Process macro were performed. Results revealed that higher pain intensity was associated with higher pain catastrophizing (β = 1.88; 95% CI: [1.00, 2.75]) and lower pain resilience (β = -0.36; 95% CI: [-0.47, -0.25]), which in turn was associated with greater pain interference (β = -0.10; 95% CI: [-0.14, −0.07]), and lower physical (β = 0.18; 95% CI: [0.02, 0.35]) and mental (β = 0.61; 95% CI: [0.43, 0.80]) HRQoL. These findings suggest that targeting pain catastrophizing and pain resilience may help mitigate the negative impact of pain intensity in adults with CMP.

Phases of Authentic Relationship-Building with Black Communities for Sustainable Partnership in Chronic Pain Research
De'Sha Wolf; Portland State University

Nearly 20% of non-Hispanic Black adults experience chronic pain, and their disability rates are 2.5 times higher than White adults in some metro areas. Black patients are also routinely under-enrolled in clinical research studies that can improve pain outcomes. To mitigate these disparities, Black adults must be uplifted as experts of their own care in the communities they live in, and participate in pain intervention development processes. A community-based approach is critical for those in predominantly white cities, where culturally-responsive services are limited. This poster will present a three-phased process of authentic relationship-building with Black communities partnering in chronic pain research, education, and advocacy. Data will be extracted from: 1) an NIGMS-funded pilot study using an asset-based approach to clinical research that uplifts young Black adults with chronic pain, and 2) a 2024-2025 USASP Leadership Academy Capstone project that facilitates community-based solutions for Black Portlanders living with chronic pain. Phase 1 presents Black clinical research participants' opinions of the pain research questions most important for improving quality of life and

preventing pain-related disability. Phase 2 provides creative strategies for investigators with limited resources to develop sustainable partnerships with community gatekeepers, organizations, and clinics. Phase 3 presents a preliminary community strategic plan featuring upstream-downstream interventions, services, and advocacy priorities to reduce the burden of pain in Black adults' lives. Results will demystify the hows of stakeholder engagement in pain research, and elevate the expertise of experienced Black clinical research participants. NIH (RL5GM118963 and K01AT012905), and the PSU Faculty Development Program.

Clinical Trials for Pain Research

Feasibility of Group Format Pain Reprocessing Therapy in Veterans with Chronic Back and Neck Pain
Zan Wynia, Yoni Ashar, Charlotte Nolan, Leon Cox, Joseph Frank; University of Colorado Anschutz Medical Campus

Veterans experience chronic back and neck pain (CBNP) at twice the rate of civilians. Pain Reprocessing Therapy (PRT) is a promising individual format treatment with demonstrated efficacy for backpain in civilians, but its acceptability among veterans is unknown. We conducted an uncontrolled pilot trial of a novel telehealth group-format PRT intervention in a population of veterans with CBNP. This study was conducted at the Veterans Affairs Eastern Colorado Health Care System (VA ECHCS) from May-November 2024 with 4-month follow-up completed for all cohorts by January 2025. We enrolled four cohorts of participants (8-16 participants each). PRT was delivered by two experienced therapists for 8 sessions over Webex. The primary feasibility outcome was session attendance, and the primary clinical outcome was last-week average pain severity (numerical rating scale from 0 to 10, from the PEG scale) at the 4-month post-baseline timepoint. Focus groups were conducted after each cohort to solicit recommendations to improve participant experience. A total of 47 participants enrolled in the study, 4 dropped out prior to starting treatment and 4 attended only one group. Of the remaining 39, 82% (32) attended at least 7/8 sessions. Clinical outcomes and focus group results will be available January 2025 after follow-up has been completed. This study investigates the scalable potential of PRT by adapting it to group format delivered using telehealth, with potential applications to both veteran and civilian contexts. Limitations of the study include the uncontrolled design, small sample size, and short follow-up.

Pictorial Representation of Illness and Self Measure: A Putative Transdiagnostic Tool for Evaluating Therapeutic Effects of Psilocybin-Assisted Therapy in Fibromyalgia
Niloufar Pouyan, Jacob Aday, David Williams, Kevin Boehnke, Steven Harte; University of Michigan

Individuals with refractory conditions like fibromyalgia (FM) will often strongly identify with their illness, affecting their quality of life. The Pictorial Representation of Illness and Self Measure (PRISM) assesses the degree of enmeshment between one's self-identity and one's illness by quantifying "self-illness-separation" (SIS) distance (Büchi et al., 2002; Paschali et al., 2021). A higher SIS distance indicates lower self-identification with illness. Our recent

epidemiological survey of 297 adults indicated that psilocybin-assisted therapy (PAT) reduces self-illness enmeshment (i.e., increasing SIS distance), correlating with symptom improvements across several diagnoses, including depression, anxiety, and PTSD—conditions frequently comorbid with FM (Pouyan et al., 2024, under review). To further investigate this phenomenon, we assessed self-illness enmeshment using the PRISM tool in a case series of FM patients undergoing PAT. Among the four participants who completed the PRISM, 75% showed increased SIS distance scores, indicating reduced self-identification with FM, consistent with their subjective reports of improvement. Participant 001, who reported being 'much improved,' saw SIS scores rise from 2.7 to 18.4, while participant 003, also 'much improved,' experienced an increase from 5.9 to 12.8. In contrast, participants 002 and 004, who reported being 'minimally improved,' showed smaller changes, from 0.8 to 5.2 for 002, or mixed trajectories as seen with 004, whose scores initially rose from 12.1 to 16.9 but dropped to 8 at follow-up. Taken together, preliminary results suggest that PRISM has transdiagnostic sensitivity and shows potential to gauge treatment response for treatments such as PAT in multidomain disorders like FM.

Leveraging Painimation and Machine Learning to Identify Predictive Features of Chronic Pain

Nahom Mossazghi, Jude Jonassaint, Joel Disu, Charles Jonassaint, Sossena Wood; Carnegie Mellon University

Pain assessment remains largely subjective and reliant on tools that struggle to capture the full complexity of the pain experience in patients suffering from chronic pain. Conventional assessments offer limited insight into the patterns and features that define chronic pain and are not ideal for facilitating patient comprehension. Painimation, a novel digital pain assessment tool, uses dynamic animations and a paintable body image to measure pain quality, intensity, location, and the body area affected by pain (quantified by pixels selected). Using machine learning and data collected from Painimation, we sought to identify and later predict key features of pain in adult chronic pain patients. In this study, 189 participants from a chronic pain clinic, all reporting pain more days than not for at least three months, completed Painimation assessments alongside demographic surveys. Machine learning models, including linear regression, random forest, gradient boosting, and neural networks, were trained to predict participants' self-reported pain levels (0–10 scale). The random forest model outperformed others (MSE = 2.76, r = 0.05), enabling feature importance analysis. This analysis identified lower back pain, age, and descriptors such as "throbbing," "electrifying," and "shooting" as the most predictive features, highlighting their potential as biomarkers of chronic pain. While data sparsity within the dataset presented challenges and contributed to low correlation values, ongoing efforts to optimize our methodology aim to mitigate these effects and enhance predictive power. These findings underscore the potential of machine learning to advance our understanding of chronic pain mechanisms and improve management. K23 HL135396 (PI: Jonassaint) from the National Heart Lung and Blood Institute and the Virginia Kaufmann Foundation.

The ePainSupport Digital Application for Assessing Pain and Pain Management in Home Hospice: A Randomized Controlled Trial

Masako Mayahara, Joellen Wilbur, Louis Fogg, Mary Clare Houlihan, Jacquelyn Benson, Debra Parker Oliver, Arlene Miller; Washington University in Saint Louis

Background. Poor pain management in home hospice is associated with lack of adherence to patient pain management regimens by family caregivers. Healthcare technology can improve caregiver access to education and communication to hospice nurses. Objective. The study purpose was to (1) compare the effects of the e-PainSupport intervention for family caregivers on change in patient pain intensity from baseline to 14 days to the effects of a standard care control condition, and (2) examine mediating effects of pain management knowledge, self-efficacy, and adherence to pain medication regimen on change in patient pain intensity, controlling for study condition and patient gender.Methods. This was a two-group, two-week, randomized controlled trial with dyads (N = 44) of patients (52% female, mean age 74.1 years) and their caregivers (75% female, mean age 55.2 years) randomly assigned to either the e-PainSupport intervention or standard care control condition. e-PainSupport included caregiver pain education, pain assessment and management tracker, and communication to nurses. Participants were recruited from four hospice agencies in a large metropolitan area. Outcome measures included caregiver knowledge, self-efficacy, medication adherence, and patient-reported pain intensity.Results. The e-PainSupport intervention produced a small positive effect on reducing pain intensity ($d = 0.27$) and a statistically significant increase in adherence ($p = 0.003$), as compared to standard care. Hierarchical regression models showed a significant mediating effect of increased caregiver knowledge on reducing pain intensity ($p < 0.01$), regardless of condition. Conclusions. e-PainSupport is feasible, and data indicate that it contributes to decreasing pain in hospice patients.

Improving Design and Execution of Non-Pharmacologic Chronic Pain Intervention Trials: Lessons Learned from an Randomized Controlled Trial of Yoga vs. Stretching for Chronic Low Back Pain

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Non-pharmacologic interventions for pain management have demonstrated efficacy in reducing pain in clinical trials. However, many trials have high attrition and lack robust research designs. Advancing designs for future non-pharmacological pain management trials by building upon successes and challenges in previous trials is of utmost importance. Drawing from our ongoing RCT examining two non-pharmacologic interventions for chronic low back pain (CLBP), we outline considerations for clinical trial design methodology spanning recruitment/enrollment, intervention execution, assessments, and multidisciplinary study teams to guide future research. Our RCT comprises 204 participants with CLBP (Mean age = 43.4, 62.7% female, 73.5% White) who engage in a 12-week intervention of either yoga or stretching. We report specific examples from this RCT to support each lesson learned including: (i) ways to assess and address participant “buy-in”, (ii) ideas for targeted recruitment efforts, (iii) suggestions for utilizing techniques such as motivational interviewing throughout the intervention to maximize engagement and limit attrition, and (iv) considerations for maintenance of treatment gains via relapse prevention strategies. We support these considerations with data collected from our RCT;

for instance, the Credibility/Expectancy Questionnaire indicated that 34.8% of the sample responded between “not at all” and “somewhat” when asked about how logical the treatment seems, highlighting the need to consider participant buy-in. These insights informed by our ongoing RCT provide guidance on the trade-offs and action steps for researchers to optimize the design and methodology of non-pharmacologic pain intervention trials.

Long-Term Efficacy Of Digital Acceptance And Commitment Therapy For Fibromyalgia: Follow-Up Of The PROSPER-FM Trial At 12 Months

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Fibromyalgia (FM) is a chronic pain condition that significantly impacts quality of life. The FDA-cleared digital Acceptance and Commitment Therapy (ACT) program, Stanza™, was developed to provide self-guided ACT for patients with FM. Its safety and efficacy were validated in the PROSPER-FM phase 3 randomized controlled trial, which demonstrated significant improvements in patient wellbeing, FM severity, and other FM-related symptoms at 12 weeks compared to an active control (Gendreau, 2024). Building on these findings, the PROSPER-FM extension study evaluated the 12-month durability of symptom improvement of digital ACT. The extension study enrolled 60 completers from the digital ACT arm of the PROSPER-FM study, who continued using digital ACT as needed. The response rate on the primary outcome measure (minimally improved or better on the Patient Global Impression of Change) remained stable from week 12 (80.0%) to month 12 (79.6%). Significant improvement from baseline on the Revised Fibromyalgia Impact Questionnaire (FIQ-R) was maintained from week 12 (mean improvement [SE]: -12.1 [1.7]) to month 12 (mean improvement [SE]: -12.4 [2.4]). Additional clinical benefits significant at 12 weeks that were sustained at 12 months included improvements in FIQ-R sub-domains, pain intensity, pain interference, sleep interference (0-10 numerical ratings scale), PROMIS-Fatigue, PROMIS-Sleep Disturbance, and Psychological Inflexibility in Pain Scale. These results demonstrate that Stanza yielded long-term benefits for FM patients, with improvements in both symptoms and function that persisted for 12 months. The study supports digital ACT as an accessible and efficacious non-drug treatment with durable results for FM.

Heterogeneous Treatment Effects of Transcranial Direct Current Stimulation on Knee Osteoarthritis Pain and Symptoms

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Although transcranial direct current stimulation (tDCS) has been widely reported as a safe and effective brain stimulation technique for managing knee osteoarthritis (KOA) pain and symptoms, studies indicate significant variability in treatment effects among individuals. This study aimed to identify the predictors of such heterogeneity in older adults with KOA receiving tDCS, with the goal of enhancing personalized treatment strategies. This secondary analysis of a randomized clinical trial included 60 participants with symptomatic KOA who underwent 15

daily sessions of 2-mA active tDCS (20 minutes per session) over three weeks. Initially, a multi-trajectory latent class growth analysis was conducted to identify salient patient groups based on the longitudinal trajectories of key symptom parameters—pain severity as per the Numeric Rating Scale, and the pain, stiffness, and physical function subscales as per the Western Ontario and McMaster Universities Osteoarthritis Index—from baseline to the 3-month follow-up post-intervention. Two distinct trajectory groups were identified: Group 1 (n = 29, "Low initial symptoms with considerable improvement"); and Group 2 (n = 31, "High initial symptoms with minimal improvement"). Thereafter, bivariate analysis examined associations between the trajectory groups and baseline sociodemographic and clinical characteristics. Compared to Group 1, individuals in Group 2 were less likely to have higher educational attainment, had a higher body mass index, and exhibited greater pain catastrophizing, punctate mechanical pain, temporal summation of pain, and impaired conditioned pain modulation (all $p < .05$). Characterizing these predictive factors can help in developing personalized tDCS protocols for KOA, potentially enhancing treatment effects.

One Size Fits Some: Identifying How A Telehealth Delivery System Impacts Patient Experience

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Telehealth treatment delivery improves access and reduces burden, but low patient engagement and attrition limit use. Identifying factors associated with positive telehealth treatment experience could guide treatment refinement and improve treatment outcomes. Post-treatment qualitative interviews with a purposive sample of treatment completers and non-completers (N=20) assessed experiences in a clinical trial of an asynchronous, cognitive-behavioral therapy for chronic pain (CBT-CP) intervention. In treatment, participants used a manual to learn one CBT-CP skill per week and received daily, automated surveys via phone call to assess nine skill practice and pain-relevant variables. Once weekly, participants received a recorded feedback message from a coach that was personalized based on the participant's daily survey ratings. Individual interviews were conducted by phone and transcripts were analyzed using an open coding approach. This analysis revealed polarized views on two aspects of intervention delivery: the daily calls and asynchronous feedback. Although many viewed the daily calls positively, as a reminder and a means to promote accountability for practicing CBT-CP skills, others found the daily calls burdensome and disliked answering the same questions each day. Most participants had neutral opinions regarding the asynchronous coach feedback, but several participants had strong negative feedback, finding the asynchronous coaching impersonal and expressing the need for real-time coach interactions. These findings suggest discussing treatment delivery elements with patients prior to referral may be necessary to ensure a good fit. Further, broad advancement of telehealth treatments will require examining the role of specific treatment delivery elements in acceptability and outcomes.

Role of DHEA and DHEA-S on Cold Tolerance and Thresholds in Adolescents

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Adolescence is marked by puberty-related changes, including significant shifts in sex hormone levels. Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEA-S) are less studied compared to the other sex hormones and their role on experimental pain is unclear. This study investigated the relationships between androgen levels and cold pain sensitivity in healthy adolescent girls. Forty-five healthy girls (11.91 ± 1.35 years, range 9 - 15 years) participated in the study. Participants completed a study visit which included assessing their cold pain threshold and tolerance and completing the Pubertal Developmental Scale. Blood samples were collected for analysis of androgen levels. Separate regression models assessed the relationships between androgen levels and cold pain sensitivity. In addition, androgen levels were compared between adolescents who were pre-menarche vs. menarche and whether menarche status moderated the androgen-pain relationships was also tested. DHEA and DHEA-S were both inversely associated with the cold pain threshold (r2=0.088, p=0.050 and r2=0.093, p=0.049, respectively), indicating an antinociceptive effect. DHEA and DHEA-S levels were significantly higher in the menarche group compared to the pre-menarche group. However, no interaction effects were observed. For cold pain tolerance, a significant positive relationship was found only with DHEA-S (r2=0.118, p=0.026), indicating an antinociceptive effect. Furthermore, an interaction effect was found, indicating that DHEA-S levels significantly related to cold pain tolerance in the menarche stage (r2=0.113, p=0.030) compared to the pre-menarche stage.

Trajectories of Pain Impact and Pain Self-Efficacy in People with HIV and Chronic Pain: Extending Findings from the Skills TO Manage Pain (STOMP) Randomized Clinical Trial

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People with HIV (PWH) commonly experience chronic pain, which leads to poor health outcomes. Thus, we need evidence-based interventions that address chronic pain in the population. Skills TO Manage Pain (STOMP), a pain self-management (PSM) intervention tailored for PWH and chronic pain, demonstrated efficacy by decreasing pain impact (the overall effect of pain on an individual) and increasing pain self-efficacy (an individual's belief in their ability to engage in activities to manage pain) immediately following the intervention and three months later. We evaluated whether STOMP's impact on pain and self-efficacy persists over 12 months among 244 adults (49% female, Mage = 53.62) with HIV and chronic pain randomized to STOMP or Enhanced Usual Care (EUC). We also evaluated whether pain self-efficacy mediates the association between treatment condition and changes in pain impact. Compared to EUC, individuals in STOMP reported lower pain impact and higher pain self-efficacy over twelve months. The STOMP group maintained improvements in pain impact over twelve months, but the EUC group also gradually improved, leading to slightly attenuated differences in pain impact between the groups over time. Compared to EUC, individuals in STOMP maintained significantly higher pain self-efficacy over time, and they demonstrated greater improvements in their confidence to manage pain, leading to less severe pain and reduced interference in daily activities. STOMP is efficacious for chronic pain for PWH up to one year following the

intervention. Researchers should continue to explore mechanisms of change and best practices for implementing STOMP in diverse groups and care settings.

Intradiscal Administration of STA363 In Patients With Radiculopathy Caused by Lumbar Disc Herniation Reduces Disc Volume Predictive of Symptomatic Relief

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Introduction. Previous phase 1 and 2b studies in patients with degenerative disc disease (DDD) show that STA363 dose-dependently reduces disc height and dehydrates the nucleus pulposus (NP), suggesting a chemonucleolytic effect of STA363 in the treatment of symptomatic lumbar disc herniation (LDH). The present study was conducted to establish safety and tolerability in LDH patients, and to assess the effects on disc volume, height and water content (intensity of NP via T2-weighted MRI).
Methods. In a placebo-controlled, randomized, double-blind, parallel design phase 1b study on 25 patients with LDH, STA363 (S-lactic acid (120 mg/mL) in Omnipaque, 1.5 mL, 17 patients) or placebo (1.5 mL of Omnipaque, 8 patients) was injected into the symptom-generating herniated lumbar disc (Pfirrmann grade ≤3). The patients were followed for up to 6 months with double echo MRI at baseline, 1, 3 and 6 months. The primary objective was to assess safety and tolerability with secondary/exploratory objectives including disc volume, midsagittal disc height and NP water content (T2-time, msec). The analysis of disc height and volume (calculated from sagittal disc heights) was done by experienced radiologists and T2 times were quantified by image analysis experts, all blinded to the treatment allocation. Further, appearance of, or changes in existing Modic changes were evaluated by the radiologists.
Results. Seventeen men and 8 women were included with a mean age of 38±7 years and a mean BMI of 26±4 kg/cm^2). Three injected discs were at L3/4, 13 at L4/5 and 9 at L5/S1. Twentyfour discs were Pfirrmann grade 3 and 1 was grade 2. Safety and tolerability were similar to that previously established in DDD patients. Baseline disc volume (mL) in the placebo and STA363 groups was 14.4±3.0 (mean±SD) and 12.6±2.9, respectively. The change at 1, 3 and 6 months was -0.20±0.40, -0.34±0.45 and -0.39±0.54, respectively (placebo), and -0.86±0.98, -1.40±1.15 and -1.53±1.55, respectively (STA363). Baseline disc height (mm) in the placebo and STA363 groups was 11.4±1.3 and 11.1±1.7, respectively. The change at 1, 3 and 6 months was -0.28±0.31, -0.33±0.43 and -0.17±0.37, respectively (placebo), and -0.58±0.92, -1.13±1.06 and -1.27±1.14, respectively (STA363). Changes in disc height and volume were correlated in the STA363 ($p=0.03$) but not in the placebo group ($p>0.05$). Mean baseline T2 times (msec) were 72.1±8.2 (placebo) and 83.3±19.3 (STA363). The change at 1, 3 and 6 months was -3.1±4.5, -3.3±6.6 and -4.9±6.3, respectively (placebo), and -7.4±13.0, -10.9±15.5 and -12.1±16.0, respectively (STA363). Existing Modic changes (n=4 (placebo) and n=7 (STA363)) did not change, nor did the prevalence of Modic changes increase.
Discussion. STA363 produces a reduction in disc volume, which is similar to that of other chemonucleolytics with established pain reduction used clinically. Volume decrease is seen after 1 month and seems to stabilize between 3 and 6 months. STA363 does not appear to induce Modic changes. The effects of STA363 on symptoms in LDH patients will be addressed in future studies powered for that purpose.

From Chronic to Acute Pain: Evaluating Baseline Prognostic Covariates in Severe Acute Lower Back Pain

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The FDA's 2023 guidance on baseline covariate adjustment highlights the importance of incorporating prognostic covariates into randomized clinical trials (RCTs) efficacy analyses. Adjusting for such covariates can reduce variability in treatment effect estimates, leading to narrower confidence intervals and more powerful hypothesis testing. In line with this guidance, Placebell baseline prognostic covariates were developed for chronic pain indications. The Placebell covariates, derived from chronic pain RCTs, integrate baseline factors such as disease severity, psychological traits, and demographics. This study aimed to evaluate the applicability and benefits of these covariates in an acute pain indication: severe acute lower back pain (LBP). Their impact on the analysis precision was assessed in a phase II trial of severe acute LBP (SP-103-02 sponsored by Scilex Pharmaceutical). The primary endpoint was the time-weighted Summed Pain Intensity Difference (SPID) score, calculated as the change from baseline in daily average pain scores (Days 1-7). Precision improvement was quantified by comparing the primary analysis model to the same model adding the Placebell covariates. Including these prognostic covariates increased the precision of the treatment effect estimate by 34.75% ($p<0.001$). Having the same precision without them would have required adding 25 patients to the 72 per protocol from the study. As such, the Placebell covariates, designed to account for contextual effects, demonstrated robust transferability from chronic to acute pain settings. By significantly enhancing assay sensitivity, they offer a practical approach to improving precision equivalent to a larger sample size in acute pain RCTs.

Associations Between Increased Use of Nondrug and Integrative Modalities and Reduction in Pain and Opioid Dose in Veterans with Chronic Pain and Posttraumatic Stress Disorder

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Co-occurring chronic pain and posttraumatic stress disorder (PTSD) are associated with poorer outcomes. Nondrug therapies (NDTs, e.g., yoga) are first line for chronic pain, but effects among patients with co-occurring PTSD are unknown. From 2017 to 2021, 820 patients with chronic pain prescribed long-term opioids enrolled in the VOICE trial across 10 VA sites. Participants were randomized to one of two interdisciplinary pain care interventions. NDT use, Brief Pain Inventory (BPI) scores, and opioid dose were assessed at baseline, 6-, and 12-months. NDTs were categorized as manual (e.g., acupuncture), movement (e.g., tai chi), and behavioral therapies (e.g., meditation). Adjusted multivariable repeated measures regressions modelled associations between increases in NDT use of ≥1 therapies and changes in pain and opioid dose from baseline at 6- and 12-months. Two hundred participants (24%) had probable PTSD at baseline. Both pain care delivery interventions resulted in significant increases in NDT use. Among participants with co-occurring chronic pain and PTSD, an increase in the total number of NDTs used was positively associated with a 30% reduction in BPI total score at 12 months [Odds Ratio (OR)=2.82 (95% Confidence Interval (CI)=1.03-7.71); p=0.044] and increased manual

therapy use was associated with a 30% reduction in BPI severity at 6 months [OR=4.64; 95% CI=1.19-18.17; p=0.028]. Increased use of movement therapy was associated with a 25% reduction in opioid dose at 12 months (OR=2.01, 95% CI=1.10-3.70; p=0.024). Among participants with co-occurring chronic pain and PTSD, increased use of NDTs was associated with decreases in chronic pain and opioid dose.

A Pilot RCT of a One-Day Acceptance and Commitment Therapy Workshop for the Prevention of Post-Surgical Pain Following Spine Surgery

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Approximately 20% of patients undergoing spine surgery experience chronic postsurgical pain (CPSP). Psychological interventions may help prevent CPSP but are costly and burdensome leading to poor access and adherence and difficulty in perioperative implementation. Brief acceptance and commitment therapy (ACT) has resulted in faster cessation of pain and improved function in surgical studies. However, this has not been assessed in spine surgery. The aim of the current pilot randomized controlled trial was to assess the preliminary efficacy of brief perioperative ACT intervention to prevent CPSP. Adults (N=xx) scheduled to undergo spine surgery were assigned to a 1-day ACT workshop + or treatment as usual (TAU). They reported pain intensity and interference, anxiety, and depression using PROMIS-29 at baseline and three months post-surgery. Results of repeated measures ANOVAs indicate significant effects of time such that participants showed improvement in pain intensity and interference from baseline to three-month follow-up regardless of treatment group. There were no time by treatment interactions suggesting that those in the ACT group did not show greater improvement than those in the TAU group. However, there were trends in the time by treatment interactions for both depression and anxiety suggesting that patients in the ACT group showed an improvement in depression and anxiety from baseline to follow-up while there were no changes in the TAU group. Despite null findings, these results may suggest a need for identifying and targeting those at high risk for CPSP such as those with high levels of depression, anxiety, and catastrophizing preoperatively.

The Validity and Usefulness of a Modified Brief Pain Inventory for Individuals with Knee Osteoarthritis

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Knee osteoarthritis (KOA) is one of the most common causes of pain and disability worldwide. The Brief Pain Inventory (BPI) is commonly used to assess symptom severity in individuals with KOA. However, the BPI's pain intensity subscale may underrepresent symptom severity due to the inclusion of the item assessing "least pain." The purpose of this study was to examine the internal consistency, model fit, and convergent validity of a modified BPI that replaces the "least pain" item with an item related to pain interference when walking among individuals with KOA. Data from 279 individuals with KOA from two clinical trials were analyzed; 242 undergoing total knee arthroplasty (NCT01370421) & 37 in a randomized, double-blind, 2-way crossover,

placebo-controlled study of COX-2 inhibitors (NCT01619150). The modified BPI subscale showed excellent model fit (Comparative Fit Index = .99; Tucker-Lewis Index: .98-.99; Root Mean Square Error of Approximation: .08-.001), good internal consistency (Cronbach's alpha: .84-.87) and high convergent validity with the Pain Catastrophizing Scale ($r = .50$, $p < .001$) and the Western Ontario and McMaster Universities Osteoarthritis Index ($r = .66$, $p < .001$). Additionally, contrary to the original subscale, the modified BPI subscale did not result in a floor effect following total knee arthroplasty. The psychometric properties of the modified BPI were comparable to or better than those produced by the original BPI pain intensity subscale. The modified BPI may be helpful in assessing symptom severity of KOA, more closely capturing symptoms that drive patients to seek clinical care.

Exploration Of Associations Between Expectations And Pain Improvement In Painful Peripheral Neuropathy Clinical Trials

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The demonstration of efficacy for therapies of chronic pain has been hindered by decreasing treatment effect sizes in randomized clinical trials (RCTs). Reducing variability in outcomes could improve detection of treatment effects. We hypothesized that participants' baseline expectations for improvement with treatment are associated with pain RCT outcomes and could be controlled for in future analyses to reduce variability. This secondary analysis used data from a 6-week multi-site placebo-controlled RCT of Transcutaneous Electrical Nerve Stimulation (TENS) for Chemotherapy-Induced Peripheral Neuropathy (CIPN). Participants reported the intensity of 3 pain qualities (hot burning pain, sharp shooting pain, and cramping), reported their expectation for improvement, and were randomly assigned to either TENS or placebo treatment groups. Expectation was assessed by asking [How likely do you think it is that a TENS device can improve your neuropathy symptoms?] 1 [Not at all likely] to 5 [Very Likely] and responses were dichotomized into low (ratings 1-3) or high expectation (ratings 4-5). Analyses of covariance tested the impact of baseline expectations on a previously-reported personalized pain outcome. Expectation was significantly associated with the pain outcome at study endpoint ($t = 2.089$, $p = 0.0408$). However, no significant difference was found between treatment groups regarding the correlation of expectations and pain outcomes ($t = 0.032$, $p = 0.9743$). These findings suggest that accounting for baseline expectations could reduce outcome variability in neuropathic pain trials, improving the ability to detect treatment effects. Further analyses with additional trials are needed for validation. Funded by NIH (R21CA235389; UG1CA189961, K24NS126861).

Patient Perspectives on the Summit Opioid Tapering Support Program

Alexis Grant, Danielle Wesolowicz, William Becker, Liana Fraenkel, Manik Chhabra, Brent Moore, Sara Edmond; PRIME Center

Clinical guidelines discourage long-term opioid therapy (LTOT) for chronic pain and recommend prescribers consider tapering in cases where potential harms outweigh benefits of

continued LTOT. The Summit program offered patients with chronic pain prescribed LTOT the opportunity to engage in a supportive, patient-centered tapering program which included education, video testimonials, self-management skill-building, and access to a peer specialist. Of the 64 enrolled participants in the pilot randomized trial evaluating Summit, 22 participants provided feedback about their experience in the program via semi-structured exit interviews conducted by study staff. Guided by the constant comparison method, two coders (AG and DW) completed qualitative analysis of the exit interviews. Analysis included two phases: first, an open coding phase in which recurrent, salient themes were identified and coders met frequently to develop an initial code list, and second, a focused coding phase, during which the refined codes were applied to all exit interview transcripts. This iterative process led to identification of major themes in the data and provided a framework to report participants' perspectives on the Summit program. Participants identified several take-aways related to their engagement in the Summit program. Emergent themes included (1) the positive emotional impact of consistent communication with study staff and (2) improved medication management as a result of a changed relationship to pain and opioid use. Findings from this qualitative analysis of participant perspectives on the Summit program will inform the development of future patient-centered tapering support programs. Funding: VA HSR IIR 17-228 (PI: Becker)

Single-Session Group Breathwork Intervention for Adults with Chronic Pain: A proof-of-concept study of Guided Respiration Mindfulness Therapy

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Chronic pain is a major public health problem. Due to the persistent, costly, and complex nature of chronic pain, there is an urgent need for safe and effective treatments. Respiration is a vital physiological function that is also bidirectionally related to pain, stress, and emotions. Breathwork, or the conscious control of breathing for therapeutic purposes, has promise as a novel treatment for chronic pain. The primary objective of this proof-of-concept study was to examine the acceptability and clinical significance of a single breathwork session for adults with chronic pain. The breathwork intervention is called Guided Respiration Mindfulness Therapy and involves a sustained (1-hour) conscious connected breathing pattern where there is no pause between inhale and exhale. Participants included 11 adults with various types of chronic musculoskeletal pain. We found that the group breathwork intervention was highly acceptable and satisfying. A clinically significant improvement (i.e., $\geq$ 2-point change) in average pain intensity and interference over the past week was observed in 5 out of 9 participants at the 2-week follow-up (55.6%) and 6 out of 9 participants at the 6-week follow-up (66.7%). It is plausible that this type of breathwork intervention could produce clinically meaningful effects for those with chronic pain. Future research will examine the efficacy and biopsychosocial mechanisms of this intervention. Funding: K01AT012066 from the National Center for Complementary and Integrative Health.

An Analysis Of The Patient-Centered Outcomes Research Institute's Comparative Clinical Effectiveness Research Portfolio On Pain Management

Jillian Nowlin, Danielle Riley, Erin Colligan, Mandy Rounds, Golda Houndoh, Kathryn Martucci, Vita Pierzchala, Neeraj Arora; Patient-Centered Outcomes Research Institute

This project aims to synthesize the Patient-Centered Outcomes Research Institute's (PCORI) portfolio of funded comparative clinical effectiveness research (CER) focused on managing pain, based on a conceptual framework developed in conjunction with landscape scans and significant input from multidisciplinary community partners. The framework depicts the breadth of CER opportunities spanning the care continuum, from pain prevention through treatment and management. An algorithm was developed to assess study eligibility for inclusion in the portfolio, which was then analyzed according to the framework and classified by various characteristics including study design, condition, and intervention type. To date, PCORI has invested $380 million to fund more than 80 CER projects focused on managing pain. Of the studies analyzed, approximately 72% are randomized controlled trials. Studies conducted in neurological disorders constitute 21% of the portfolio, followed by cancer (17%), musculoskeletal disorders (17%), and rare diseases (11%). Approximately 55% of studies have included system-level interventions, followed by nonpharmacologic (48%) and pharmacologic (29%) approaches. As studies often include multiple types of interventions, these numbers aren't mutually exclusive. PCORI's pain management portfolio addresses a wide range of challenges faced by patients, caregivers, healthcare providers, and the wider healthcare community with each CER project aiming to improve patient-centered outcomes for those living with pain. Detailed feedback from community partners and our portfolio analysis indicate further CER is needed in a variety of areas, including but not limited to, urogynecological and pelvic pain, neuropathic pain, sickle cell pain, and pain experienced by those living with limitations in cognitive functioning.

Enhancing Pain Relief: The Role of Repeated Conditioned Pain Modulation and Mind-Body Interaction

Priyanka Rana, Mike Robbinson, Meryl Alappattu, Joseph Riley, Donovan Lott, Mark Bishop; University of Texas at El Paso

Enhancing Pain Relief: The Role of Repeated Conditioned Pain Modulation and Mind-Body InteractionRana P, Robinson M, Alappattu M, Riley J, Lott D, Bishop M; University of Texas at El PasoConditioned pain modulation (CPM) assesses diffuse noxious inhibitory control where one pain stimulus reduces the perception of another (Sirucek et al., 2023). Repeated painful stimuli reduce reported pain intensity, likely due to frequent activation of pain-inhibiting systems (Hoeppli et al., 2022). Therefore, repeated CPM engagement may improve endogenous pain inhibition and enhance pain relief. Psychological factors like anxiety and depression can alter pain perception (Munneke et al., 2020)and likely influence responses to painful stimuli. This study aimed to determine the extent to which repeated exposure to CPM induction modifies CPM efficiency and its association with psychological factors.60 healthy participants aged 18 to 75 years were randomly assigned to three groups: HE (4 CPM interventions, 5 sessions), LE (1 CPM intervention, 2 sessions), and NE (no CPM intervention, 2 sessions). CPM served as both intervention and assessment, with cold water as the stimulus for interventions and heat for CPM efficiency assessment. CPM efficiency and psychological factors were measured before and after the training protocol.Both the HE and LE protocols improved CPM efficacy. The frequency of

intervention (HE with 4 sessions, LE with 1 session) did not differentially affect the observed changes in CPM efficiency. Furthermore, psychological factors did not influence these results. This novel study demonstrates that CPM-targeted interventions can enhance endogenous pain regulation.

Pilot Randomized Controlled Study of Vitamin D and Omega-3 Fatty Acids to Reduce Chronic Pain After Thermal Burn Injury

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Burn injuries affect ~11 million people annually and chronic pain development is common. Low levels of n-3 polyunsaturated fatty acids (PUFAs) and vitamin D are associated with greater chronic pain following burn injury, and both have demonstrated analgesic efficacy in other disorders. The purpose of this pilot, randomized, 2x2 factorial, double-blind, placebo-controlled study was to examine the feasibility, safety, and preliminary efficacy of n-3 PUFAs and/or vitamin D administration in reducing pain in hospitalized patients with thermal burn injuries (n=24). Participants took two oral study medications daily for 6 weeks, one containing n-3 PUFAs (2 grams) or placebo and the other containing vitamin D3 (2000 International Units) or placebo. Pain severity (0-10 Numeric Rating Scale) was assessed at enrollment, weekly until 6 weeks, 3 months, 6 months, and 1 year after injury via in-person interviews and online surveys. Results support feasibility, given an excellent follow-up rate (18/22, 82% at 6 weeks; note 2 participants withdrew). The results also suggest safety, as reported adverse events were no more than minor in severity. Finally, preliminary efficacy estimates from linear mixed models adjusted for total burn surface area, sex, race, age, and baseline pain, and following outlier adjustment, indicate a statistically significant reduction in pain severity points after vitamin D treatment (β=-2.33, 95% CI [-3.76, -0.90]) but not after n-3 PUFA treatment (β=0.92, 95% CI [-0.25, 0.09]). Unadjusted models were not significant. These results are encouraging, but given the small sample size, should be interpreted with caution and call for future studies.

Moderators of the Effects of Telehealth Mindfulness-Based Interventions for Chronic Pain: a Randomized Controlled Trial

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Little is known about who benefits most from Mindfulness-Based Interventions (MBIs), and whether certain groups differentially benefit from different types of MBI formats (group-based versus non-group based). The present study uses data from a three-arm randomized controlled trial of two MBIs (self-paced and group) to test for moderating effects by gender and diagnoses of three mental health conditions (depression, anxiety, and post-traumatic stress disorder).The sample consisted of 811 veterans with moderate to severe chronic pain, recruited from three Veterans Affairs (VA) sites from 2020 to 2022. Survey data were collected at baseline and three follow-up timepoints (10 weeks, 6 months, and 12 months). Outcomes were indicators of 30% or

greater improvement from baseline in pain interference, pain intensity, anxiety, depression, PTSD, fatigue, sleep disturbance, physical function, and social functioning. A difference of 10 percentage points in intervention effect across moderator subgroups was deemed as a potentially meaningful difference.The group MBI and self-paced MBI arms had higher rates of improvement in all outcomes compared to usual care. Potentially meaningful differences were found for gender and anxiety diagnosis. In the group MBI, women had greater improvement in pain severity and depression than men, and those with anxiety diagnoses had less improvement in PTSD than those without anxiety. In the self-paced arm, those with anxiety had greater improvement in depression than those without anxiety.Certain subgroups of veterans differentially benefitted from different types of MBIs. Further research is needed to more systematically determine whether MBIs can be optimized for key subgroups.

Complementary and Integrative Pain Research

Integrating Theory of Mind Training and Acupuncture to Improve Pain Management and Quality of Life in Chronic Low Back Pain Patients: A Pilot Study
Dieu Ni Doan, Alessandra Anzolin, Arvina Grahl, Seneca Ellis, Lara Gardiner, Jeungchan Lee, Ted Kaptchuk, Vitaly Napadow; Harvard Medical School

The patient-clinician relationship is a cornerstone of integrative medicine therapies, strongly influencing treatment efficacy and quality of life. To enhance this relationship and its impact on pain outcomes, we propose a pilot study investigating the combination of theory of mind (ToM) and acupuncture as a novel approach to improve patient-clinician interactions and optimize treatment results. Six female patients (mean age: 48.5 years) with chronic low back pain (cLBP) participated, undergoing comprehensive assessments before and after the intervention, including the Patient-Reported Outcomes Measurement Information System (PROMIS), Pain Catastrophizing Scale (PCS), Perceived Efficacy in Patient-Physician Interactions (PEPPI), and Brief Pain Inventory (BPI). The intervention involved four ToM training sessions followed by one acupuncture treatment. We observed increased perceived efficacy in the interaction with the acupuncturist (PEPPI) rated by patients before and after ToM training, confirming the effectiveness of the intervention. Pain-related scales revealed improvements in physical performance, reduced anxiety and depression (PROMIS subscales), and reduced PCS scores, primarily driven by improvements in the helplessness subscale, following ToM training and acupuncture. Patients reported decreased pain severity over the week and 24 hours before the treatment compared to baseline. Although with a small sample size, this study highlights the potential of combining ToM training with non-pharmacological pain treatments of acupuncture, to bolster the physical, psychological, and social well-being of chronic pain patients, ultimately improving outcomes. Future research will include a larger sample size, brain imaging analysis using EEG data, multi-session acupuncture, and an education-based control group to validate these findings and enhance clinical applicability.

The Effects of Group Delivered Biofeedback on Peripheral Temperature and Well-Being in the Treatment of Chronic Pain
Jill Penman, Lindsay Flegge, Michael Bushey, Kristina Bogdan; Indiana University School of Medicine

Biofeedback is a complementary modality that can improve multiple pain related outcomes by addressing the contributions of the autonomic nervous system to pain propagation. Delivering this therapy typically requires specialized training, costly equipment, and a 1:1 appointment with a practitioner. To improve accessibility of biofeedback, we developed a group delivery model called Mind Meter, which consisted of pain neuroscience didactics, a guided meditation, and skin thermometer technology. We then conducted a retrospective review to assess both physiologic and subjective response to this delivery method. Participants (N=33) had various chronic pain diagnoses and were taking part in an outpatient pain rehabilitation program. During this, they participated in a onetime 2-hour Mind Meter group with 2 to 8 patients per group. Prior to and immediately after the intervention, we collected peripheral skin temperature and Adapted Edmonton Symptom Assessment Scale (ESAS) scores. Notable changes occurred in both physiologic and subjective responses. The primary outcome of peripheral temperature change showed a mean increase of 2.04°F (95% CI 0.77, 3.31; p.003). Secondarily, patients reported a reduction in pain (-1.06 points, 95% CI -0.57, -1.55; p<.001) as well as sadness, anxiety, and an increase in overall sense of well-being on the ESAS (highest p .003). There was no significant change in tiredness. These findings demonstrate that in a single group-session of Mind Meter, patients can generate measurable physiological changes attributable to alterations in the autonomic nervous system which coincide with modest pain relief. The group format provides a novel option to make biofeedback more accessible.

Patterns of Complementary and Integrative Health Therapy Utilization Among Veterans on Long-Term Opioid Therapy: A Latent Class Analysis

Maryam Kazemitabar, William C. Becker, Steven B. Zeliadt, Erica A. Abel, Haseena Rajeevan, Robert D Kerns, Anne C. Black; Yale School of Medicine

This study aimed to identify patterns of complementary and integrative health (CIH) therapy utilization among Veterans on long-term opioid therapy (LTOT) and their associations with demographic and clinical characteristics. Using electronic health records, 17,079 Veterans from a retrospective cohort on LTOT who utilized any CIH therapy between October 2021 and September 2022 at 54 VA medical centers were selected. Latent Class Analysis was employed to categorize CIH utilization patterns across nine therapies, including acupuncture, biofeedback, chiropractic care, and yoga. Sociodemographic and clinical correlates of class membership were then assessed. A four-class solution was selected based on model fit, sample distribution, posterior probability of class membership, and interpretability. Members of Class 1 (27.1% of the sample) predominantly engaged in mindfulness-based therapies such as meditation (60%) and yoga (21%). Class 2 (10.2% of the sample) was characterized by engagement in massage (100%) and acupuncture (47%). Class 3 members (30.2% of the sample) predominantly used acupuncture (100%), with minimal engagement in other therapies. Class 4 members (32.5% of the sample) exclusively engaged in chiropractic care (100%) and minimal use of other therapies. Statistical analyses revealed significant demographic and clinical differences across classes. For example, Class 1 had the highest prevalence of anxiety (21.5%) and depression (43.1%), whereas Class 4 reported the lowest rates (16.3% and 31.7%). Rurality status also varied by class; Class 3 had the highest proportion of rural members (36.3%). These findings highlight CIH use patterns

by Veterans on LTOT and suggest demographic and clinical factors influence patterns.

Barriers and Facilitators to Providers' Use of a Patient Value Identification and Goal-Setting Tool for Chronic Pain Care

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The Veterans Health Administration's (VHA) Whole Health system is shifting the focus of healthcare toward what matters most to patients. The Personal Health Inventory (PHI) assesses patient values and health goals and can facilitate patient-provider discussions to increase goal-directed engagement in multimodal pain care, but few pain patients in the VHA have completed the PHI. This study aimed to evaluate how provider characteristics were associated with experience, attitudes, barriers, and facilitators in using the PHI. A survey was administered to 114 pain management providers including pharmacists (71%), psychologists (10%), and physicians (9%); modal years in position were 1-4 years (36%) and provider age were ≤35 years (38%). Survey items assessed providers' perspectives on the utility, barriers, and facilitators for using the PHI. Exploratory Factor Analysis of survey items identified three factors: Value and Relevance of the PHI, PHI Implementation Support, and Patient Completion, explaining 63.95% of the total variance. On average, providers rated the PHI as valuable and relevant, but rated themselves as having moderate support in using the PHI, and minimal experience using it with patients. ANOVA tests revealed Value and Relevance scores differed by provider specialty, PHI Implementation Support scores differed by years of VA experience, and Patient Completion scores differed by provider age and specialty (all ps<.05), with clinical pharmacists and younger providers scoring lower on survey factors. Our findings suggest the need to support providers' skills in PHI implementation, potentially tailoring implementation efforts to provider characteristics, with an ultimate goal of improving patient-centered pain care.

Findings from the Feasibility and Acceptability of Music Imagery and Listening Interventions for Analgesia Study

Matthew J Bair, Kristin Maya Story, Barry Barker, Sheri Robb, James Slaven, Sally Wasmuth, Leah Whitmire, Dawn Bravata; VA Center for Health Information and Communication

Chronic pain is common among military veterans and is associated with disability, poor quality of life, and psychological comorbidity. The Veterans Administration (VA) recommends an integrative approach to chronic pain management and has prioritized expansion of telehealth to increase access to pain management services. Music interventions have shown promise as effective non-pharmacological options for pain, but previous studies examined less engaged music listening interventions delivered in-person for individuals with acute pain. The objective of the Feasibility and Acceptability of Music Imagery and Listening Interventions for Analgesia (FAMILIA) Study was to examine feasibility, acceptability, and preliminary effectiveness of two virtually delivered interventions vs. usual care for Veterans with chronic musculoskeletal pain. FAMILIA was a 3-arm, parallel group, pilot trial. Sixty Veterans were randomized to one of three conditions: 1) 8-weekly one-on-one Music Imagery sessions; 2) a Music Listening protocol; or

3) usual care. We assessed feasibility metrics and acceptability through interviews to assess participant experiences with interventions, including perceived benefits, barriers, and facilitators. We also explored the preliminary effects of study arms on pain and associated outcomes. Study participants were complex medically and psychologically. The feasibility metrics for recruitment, retention, delivery of study treatments in the allotted time, and completion of outcome assessments were met. The interventions were acceptable to study participants. Pain outcomes improved across all three study arms but were more pronounced in the music imagery and music listening arms. Secondary outcomes (stress, depression, anxiety, catastrophizing) improved in the music arms but worsened in the usual care arm.

Intimate Partner Violence Victimization and Perpetration Behaviors Among Individuals with Chronic Pain

Guohao Zhu, Jennifer Pierce, Meagan McBride, Alec McKheen; University of Michigan Medical School

Intimate partner violence (IPV) among individuals with chronic pain is prevalent, with high rates of victimization and perpetration affecting physical and psychological health. Research often focuses on female victims, but IPV is frequently bidirectional, and male partners may also be targets. This study explores emotional and physical IPV among chronic pain patients, assessing its impact on social, psychological, and physical functioning for both men and women. The study involved 353 participants (MAge= 40.87, SD=11.72; 83% female) with chronic pain. Latent class analysis identified five IPV subtypes: high IPV (6.2%), primarily victimization (9.6%), low IPV (44.8%), moderate emotional IPV (31.2%), and primarily perpetration (8.2%). Significant group differences were observed in perceived stress ($p < .001$), hostility ($p < .001$), depressive symptoms ($p < .001$), anxiety ($p < .001$), and physical function ($p = .032$). The high IPV group reported greater perceived stress, depressive symptoms, and anxiety compared to the low IPV group. The moderate emotional IPV subtype reported higher hostility compared to the low IPV subtype. Overall, the high IPV group experienced worse psychosocial and physical outcomes. This study highlights the prevalence and impact of IPV among individuals with chronic pain, identifying five distinct IPV subtypes with unique social, psychological, and physical challenges for both men and women. Findings suggest potential for targeted interventions addressing both victimization and perpetration to improve patient well-being. Funding: UL1TR002240.

Introducing The Michigan Veterans Cannabis Program: A Community-Based Participatory Research Model To Assess The Effectiveness Of Cannabis Products On Chronic Pain Symptoms Among Veterans

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Chronic pain affects up to 30% of U.S. Veterans. Many Veterans seek and advocate for

alternative treatments for pain management, including cannabis products. In 2018, the voters of the State of Michigan passed the Michigan Regulation and Taxation of Marihuana Act, which set aside funding to conduct clinical trials focused on understanding whether cannabis may help treat medical conditions present among Veterans and prevent Veteran suicide. Supported by these funds, the University of Michigan MIVetsCan program has engaged with Veterans throughout the research process. Veteran engagement has included eliciting advice on study designs before funding, using qualitative efforts to understand Veterans' perspectives and concerns about cannabis, and establishing a community advisory board of Veterans, clinicians, and researchers to develop Veteran-appropriate research materials and recruitment methods. This program consists of two clinical trials (n=468 each), supported by a newly developed registry of Veterans with chronic pain who are currently using or interested in using cannabis products for pain management. The first trial assesses whether oral cannabidiol (CBD) improves chronic pain symptoms compared with placebo. The second trial is a health coaching intervention informed by motivational interviewing principles and the cannabis literature that focuses on optimizing Veterans' use of medical cannabis products for pain symptoms. These virtually conducted trials are open to Veterans experiencing chronic pain who reside in any state with legal adult-use cannabis. These trials address key gaps in the cannabis and pain literature, and the registry will act as a platform for future research meant to improve Veteran health.

Integrative Care For Chronic Pain In Older Adults: Accessibility And Barriers To Acupuncture

Jessica Ding, Kareena Gooroochurn, Natoshia Cunningham, Heather Howard; Michigan State University

Chronic pain is a common and debilitating condition among older adults, with 36% of Americans over 65 reporting persistent pain (National Health Interview Survey, 2023). This high prevalence presents a significant public health challenge, particularly in the context of the ongoing opioid epidemic. In response, there has been an emphasis on integrating non-pharmacological treatments, such as acupuncture, into mainstream healthcare for chronic pain management. This study aimed to explore the accessibility of acupuncture for older adults with chronic pain. We sought to understand the barriers to integrative care and the factors influencing acupuncture utilization. We conducted semi-structured interviews (n=10) with older adults who had received acupuncture for at least one month at the Chinese Hospital in San Francisco, an integrative community hospital. We used Dedoose software for inductive thematic analysis and deductive coding to identify key themes in the interview transcripts. We identified 3 themes: (1) There are gaps in health literacy on acupuncture and integrative medicine for patients and providers alike. (2) Structural barriers, such as inadequate insurance coverage, complicate access to acupuncture services long-term, primarily affecting socioeconomically disadvantaged patients. (3) Communication gaps between acupuncturists and biomedical providers, compounded by a lack of electronic health record (EHR) integration, place the burden of coordination on patients. Addressing these barriers through educational initiatives, community outreach, improved insurance guidance, and better integration of acupuncture within EHR systems could enhance accessibility and utilization of integrative care, reducing the chronic pain burden on the healthcare system. Funding: NIH F30AT013025.

Electroacupuncture Links Nociceptive and Nociplastic Pain via Brain Activation in Fibromyalgia

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Chronic pain arises from diverse mechanisms, including nociceptive pain from peripheral tissues and nociplastic pain caused by central nervous system dysregulation. Fibromyalgia (FM), a complex chronic pain condition, displays both of these mechanisms. This study explores whether electroacupuncture (EA) targets both nociceptive and nociplastic pain in FM. Our analysis included 44 participants, with 19 receiving EA and 25 undergoing a mock laser (ML) acupuncture control treatment from a prior study (Mawla et al. 2021). fMRI data were collected during a block design of pressure pain stimuli (nociceptive) on the left thumb. Following EA, increased pressure pain tolerance correlated with reduced widespread pain ($\rho = -0.56$, $p = 0.003$), linking nociceptive and nociplastic pain mechanisms—an effect absent in the ML group. Furthermore, following EA, FM patients showed increased pressure pain-induced activation in left somatosensory cortex (S1, $T = 4.32$, $p = 0.005$), right S1 ($T = 4.66$, $p < 0.001$), precuneus ($T = 4.67$, $p = 0.001$), and cingulate ($T = 4.63$, $p < 0.001$), which was more associated with widespread pain reductions, compared to the ML group. Mediation analyses revealed that activation in these brain regions mediated the relationship between increased pressure pain tolerance and reduced widespread pain (Left S1: β[se] = -0.50 [0.28], CI = [-1.16, -0.09]), suggesting that EA engages nociceptive inputs to activate S1, leading to reductions in nociplastic pain. The linkage between increased pain tolerance and reduced widespread pain following EA highlights the interplay between nociceptive and nociplastic pain mechanisms as supporting EA analgesia for FM.

Feasibility of Integrating a Group Biofeedback Intervention into Pain Rehabilitation Programming

Lindsay Flegge, Jill Penman, Kristina Bogdan, Michael Bushey; Indiana University School of Medicine

Chronic pain affects millions nationwide, yet biofeedback—a proven, non-pharmacological treatment—remains largely inaccessible due to high costs, logistical constraints, and lack of trained providers. Mind Meter, a single-session, group-based biofeedback intervention, was developed to address these barriers by utilizing affordable equipment, integrating into existing billing structures, and enabling trained providers to treat more patients simultaneously. Mind Meter targets patients' present experience of pain, anxiety, well-being, and physiological regulation (e.g., thermal hand temperature). This retrospective study (N=57) evaluated the feasibility of integrating Mind Meter into a three-week outpatient pain rehabilitation program (PRP) from January-November 2024 using key feasibility metrics: recruitment, enrollment, adherence, and assessment. Recruitment success was 70.18%, with barriers including illness or absence from the PRP. Enrollment reached 100%, as no recruited patients declined participation. Adherence was high, with all but one participant completing the two-hour intervention. Assessment completion was 97.5% during the intervention, though a process error resulted in only 57.89% of all assessment data being fully recorded, identifying a key area for improvement.

Scheduling feasibility was demonstrated, with 15 of 16 patient cohorts successfully receiving the intervention co-led by a physician and psychologist. Consistency was high, with 14 of 15 sessions occurring on the same day and time, supporting integration into routine clinical care. Findings suggest it is feasible to implement Mind Meter within PRPs, with potential to expand access to biofeedback for chronic pain patients. Future directions include refining data collection protocols to improve assessment accuracy and ensure complete data capture.

A Scoping Review Of Nonpharmacological Interventions' Effects On Opioid Use In Chronic Noncancer Pain Management
Zhanette Coffee, Judith Gordon, and Todd Vanderah; University of Arizona

Despite limited evidence supporting their effectiveness, opioids are still commonly prescribed for long-term management of chronic noncancer pain (CNCP). However, the substantial risks of prolonged opioid use, such as dependency and the rise of unregulated opioid pills, drive both patients and clinicians to explore alternatives. There is an urgent need for nonpharmacological interventions (NPIs) that can complement or replace opioids in CNCP management. Comprehensive reviews assessing NPIs' impact on reducing opioid use in adults with CNCP are scarce, prompting our scoping review. We conducted a literature search in PubMed, CINAHL, Embase, PsycINFO, and Scopus, initially in April 2021 and updated in January 2024. This search yielded 19,190 relevant articles, of which thirty-nine met the eligibility criteria and underwent data extraction. Among these, 19 (49%) were randomized controlled trials, 18 (46%) were observational studies, and two (5%) were secondary analyses. Findings suggest that NPIs such as mindfulness, yoga, educational programs, specific devices or digital technologies, chiropractic care, and combination NPIs may effectively reduce both pain intensity and opioid use in adults with CNCP, while other NPIs, such as hypnosis and virtual reality, did not show significant effects. This review indicates a small to moderate body of evidence supporting the potential of certain NPIs as effective and safe approaches to concurrently reducing pain and opioid use.

Diversity, Inclusion, and Anti-Racism

Ecological Momentary Assessment of Chronic Pain and Hazardous Drinking Among Black Adults Through a Minority Stress Lens: The Role of Daily Microaggressions
Tanya Smit, Andrew Rogers, Jaye Derrick, Michael Businelle, Ezemenari Obasi, Andres Viana, Michael Zvolensky; University of Houston

Hazardous drinking and chronic pain are highly prevalent and frequently comorbid health conditions for which Non-Latinx Black (hereafter Black) adults face disproportionately poorer health outcomes. Racial microaggressions, defined as verbal or non-verbal indignities that insult or put down people because of their race or ethnicity, may impact alcohol use and pain among Black adults with chronic pain. The current study aimed to elucidate how daily racial microaggressions impact pain experience and alcohol use severity using Ecological Momentary Assessment (EMA) methodology. Participants were 107 (31.8% female; Mage = 28.10, SD = 4.05, age range = 22-46 years) adults who self-identified as Black and non-Latinx and endorsed concurrent chronic pain and hazardous drinking. Results indicated that after experiencing microaggressions, individuals had higher pain interference, more severe pain, more severe

alcohol cravings, and reported higher subsequent alcohol consumption. When individuals experienced more microaggressions than they do on average, they tended to experience higher pain interference, more severe pain, and more severe alcohol cravings, but not higher alcohol consumption. Individuals who experienced microaggressions more often than the sample average endorsed higher subsequent alcohol consumption. This study is the first to suggest that microaggressions impact alcohol and pain-related outcomes. Future research is needed to explore the potential of mitigating the deleterious effects of microaggressions among this health disparities group. Funding: NIAAA (F31 AA030163-01) and Society of Addiction Psychology (SoAP) Student Research Grant awarded to Tanya Smit.

Cultural, Linguistic, and Metabolic Intersections in Chronic Pain Management: Insights from a Qualitative Study

Ryan Davis, Cassie Yu, Nathan Pier, Junfeng Ma, Rita Dinh, Shinye Kim; University of Wisconsin-Madison

Chronic pain management requires a holistic understanding of patients' unique cultural, linguistic, and metabolic health needs, yet these factors are often overlooked in clinical care (Smith et al., 2023; Brady et al., 2022). This qualitative study examines the intersection of chronic pain, culture, and metabolic health through semi-structured interviews with patients and healthcare providers. Participants from diverse backgrounds shared challenges in accessing culturally tailored pain management solutions, navigating language barriers, and incorporating metabolic health factors like glucose monitoring into treatment decisions (Chen & Liu, 2023). Thematic analysis of over 20 interviews revealed key insights, including the centrality of patient self-advocacy in overcoming culturally mismatched care and gaps in provider training regarding linguistic and cultural competence (Rodriguez, 2021; Johnson & Williams, 2023). Patients emphasized how cultural dietary practices and metabolic health considerations shaped their pain management decisions, yet these were often neglected by healthcare teams. Providers highlighted the systemic barriers to integrating cultural and metabolic insights into care, including limited resources and insufficient institutional support (Garcia & Park, 2023). These findings suggest that integrating culturally and metabolically informed approaches into pain management could significantly enhance care outcomes (Thompson et al., 2022). Such strategies may foster more empathetic communication, reduce disparities in treatment, and improve the alignment of care with patients' lived experiences. This research highlights the importance of advancing innovations in pain care that address these overlooked dimensions, with implications for developing personalized, equitable strategies to benefit all communities (Newman & Thorn, 2022).

From Opium Wars to Opioid Crisis: Racialized Narratives and Implications for Pain Care Equity

Madeline Darling, Sabine LaLiberte, Hannah Swick, Shinye Kim; University of Wisconsin-Madison

This narrative review explores the sociohistorical parallels between the 19th-century Opium Wars and the contemporary opioid crisis, emphasizing their implications for advancing pain

research and care (Fisher, 2024; Pettus, 2024). The Opium Wars exemplify how British imperialism commodified and weaponized opium, devastating Chinese society and embedding addiction into racialized discourse.Similarly, the contemporary opioid crisis, including the fentanyl epidemic, perpetuates racial scapegoating, with Black, Brown, and Asian communities disproportionately stigmatized and criminalized, while white individuals are often portrayed as victims deserving treatment (Netherland & Hansen, 2016; Sussex, 2022). Historical anti-opium laws, such as the Opium Exclusion Act of 1909, disproportionately targeted Asian immigrants under the guise of neutrality (Fisher, 2024).Modern policies show similar disparities, as treatment-oriented approaches are more often applied to white opioid users than to Black or Latino communities affected by crack cocaine or heroin epidemics (Kim et al., 2020). The racialized framing of opioids and fentanyl in both periods has contributed to inequities in pain care, addiction treatment, and public health policy.Stigma surrounding fentanyl is particularly acute due to its association with overdose deaths, compounding barriers to effective treatment. Studies highlight how stigma, inadequate training, and inequitable access to care exacerbate disparities (Sussex, 2022; Boyaji et al., 2020).This review suggests that incorporating sociohistorical insights into the opioid crisis could enhance understanding of the racialized dynamics underlying addiction and pain care inequities. Such an approach may inform culturally sensitive policies, improve provider training, and guide innovative strategies to reduce stigma and disparities in pain management and fentanyl-related care.

Prevalence of Stroke and Central Pain Syndrome in a Large Health System
Sarah Alzahid, Staja Booker; University of Florida

Stroke survivors experience a number of complications that affect their quality of life, including the development of chronic central post-stroke pain or central pain syndrome (CPS). CPS is a chronic neurological condition that results from damage to the brain's pain processing pathways and causes hypersensitivity to pain. An integrated data repository of electronic medical record data, i2b2 (Informatics for Integrating Biology and the Bedside), of two geographically diverse large academic medical centers was queried to determine the prevalence of patients diagnosed with stroke (ICD-10: I60-I69) and concurrent CPS (ICD-10: G89.0). Between January 1, 2014, and December 2, 2024, a total of 111,121 patients were diagnosed with stroke and 463 were diagnosed with CPS separately. Together, a total of 248 patients were diagnosed with both stroke and CPS. Among these 248 patients, 133 (54%) were female and 110 (46%) were males, and other genders unreported. Racially, 112 (45%) patients were identified as Whites and 118 (48%) were identified as Black/African Americans, and 16 (7%) identified as other. Age distribution revealed 110 (44%) of the patients were aged 65 years and older, highlighting age as a key factor in the prevalence of these conditions. These findings emphasize the need to address demographic and potential underdiagnosis of CPS in stroke populations. Further research is needed to understand the trajectory of the CPS over time. Addressing these gaps is critical for developing targeted treatments to improve the diagnosis, quality of life, and equitable post-stroke care for groups at high risk for poor health outcomes.

An Intersectional Approach to Chronic Pain: Pain Severity and Mental Health Disparities
Alexandra Otto, Maya Joshi Delity, Amy Wachholtz; University of Colorado Denver

There is significant variability in chronic pain outcomes across sociodemographic groups, with marginalized groups often experiencing worse health outcomes. The purpose of the current study was to examine disparities in pain severity, depressive disorders, and anxiety disorders in individuals with chronic pain using an intersectional approach. The national All of Us Research Project collected electronic health records and survey data from May 2018 to February 2024, including 22,184 adults diagnosed with chronic pain conditions. Intersectional identities were quantified using an additive model, summing the number of marginalized groups an individual belonged to based on race and ethnicity, gender identity, sexual orientation, income, education, English fluency, and BMI category. Linear regression revealed that number of intersectional identities significantly predicted pain severity, $\beta = 0.37$, $p < .001$. Logistic regressions revealed a one-point increase in intersectional identities was significantly associated with a 35% increase in the odds of having an anxiety disorder diagnosis (Exp(B) = 1.34, 95% CIs: 0.33-0.38, $p < .001$) and a 39% increase in the odds of having a diagnosed depressive disorder (Exp(B) = 1.39, 95% CIs: 0.38-0.43, $p < .001$). The current study uniquely addresses chronic pain and health outcomes using an intersectional approach that extends beyond standard demographic analyses and emphasizes disparities among those belonging to multiple marginalized groups. The findings underscore the critical need for targeted clinical interventions and enhanced intersectionality training in chronic pain management. Future research should employ multivariate or multilevel analyses to examine disparities among specific intersectional identities.

Evaluating Patient Preference and Familiarity with Equity-Related Terminology in Chronic Pain Research: Insights from the PROGRESS Study

Arayam Y. Hailu, Troy C. Dildine, Brittany Dorsonne, Jessica Clifton, Emma Adair, Calia Torres, Matthias Cheung, Wendy Andrews, Elizabeth Heggan, Jackie Mierfert, Gabrielle Riazi, Regina Greer-Smith, Ting Pun, Neely Williams, Luzmercy Perez, Heather Poupore-King, Maisa Ziadni1, Sean Mackey, Beth Darnall; Stanford University

The PROGRESS Study (Pain Relief with Online Groups that Empower Skills-based Symptom Reduction) explores the effectiveness of two evidence-based behavioral treatments to manage chronic pain, with a focus on enhancing diversity, equity, and inclusion in research. Chronic pain disproportionately affects ethnic and racial minorities, as well as low-income and marginalized groups. To address these disparities, the PROGRESS Study employs a multilevel advisor infrastructure, integrating advisors with diverse lived experiences with chronic pain at every stage of the process. Our three advisory boards- our Patient Engagement Diversity Board (PEDB; N=10), Local Patient Advisory Board (LPAB; N=17), and National Patient Advisory Panel (NPAP; N=76) -foster greater representation and inclusion of historically underserved communities. A key focus in recent advisor meetings has been the evolving terminology used to describe underrepresented communities and their experiences in research and healthcare. While researchers have called for the use of patient-centered terminology and gained traction academically, it's unclear which terms patients prefer or identify with. Our self-developed NPAP online survey further explores this dialogue. Using REDCap, we surveyed 76 NPAP members to explore familiarity, comfort, and preferences for terms like "marginalized," "underserved," and "racialized." We collected and will present qualitative and quantitative data analyzed with descriptive statistics to identify trends, perspectives, and stage future research. Results will

highlight the importance of patient-centered and inclusive language to ensure respectful engagement with diverse communities. Findings will guide researchers and clinicians in adopting terminology that better reflects the preferences of individuals in these communities, advancing equity in pain care.

Expanding Access to Pain Relief Treatments for Chronic Pain: Inclusive Recruitment Methods in the PROGRESS Study

Brittany Dorsonne, Arayam Y Hailu, Kartikeya Saxena, Jessica Clifton, Emma Adair1, Matthias Cheung, Calia Torres, Wendy Andrews, Elizabeth Heggan, Jackie Mierfert, Gabrielle Riazi, Troy C. Dildine, Shelly Spears, Regina Greer-Smith, Ting Pun, Neely Williams, Luzmercy Perez, Heather Poupore-King, Maisa S. Ziadni, Sean Mackey, Beth D. Darnall1; Stanford University

Chronic pain affects over 51 million Americans (Rikard et al., 2023) and disproportionately impacts marginalized populations that are underrepresented in pain research. This highlights an urgent need for accessible treatments and the importance of intentional recruitment methods in clinical trials to ensure generalizable results. The PCORI-funded PROGRESS Study (Pain Relief with Online Groups that Empower Skills-based Symptom Reduction) is comparing two proven pain treatments, 1-session Empowered Relief vs 8-session CBT, and uses diversity-targeted recruitment strategies across 6 national sites (N=1,650). After study launch, certain demographics quickly introduced unique challenges preventing diverse participant recruitment. To increase representation, we collaborated with our diverse multilevel advisory boards - central Patient Engagement Diversity Board (PEDB; N=10), National Patient Advisory Panel (NPAP; N=76), and site-specific Local Patient Advisory Boards (LPAB; N=17) - to modify our recruitment approaches. Over a dozen recruitment methods were utilized; this poster will review our successes and lessons learned. We will present access barriers and our solutions to successfully recruit a heterogenous study population, additional steps necessary to enroll participants for an online study, and key takeaways relevant to health research broadly. PROGRESS began recruitment in January 2023 and to date 5 sites have exceeded 50% of their original enrollment goal with each surpassing their diversity recruitment goal. Despite challenges, PROGRESS is demonstrating a pathway to enrich pain research, expand behavioral treatment access to historically underrepresented populations, and disseminate our findings to patients and researchers.

Language of Pain: The Influence of Spanish-English Bilingualism and Vignette Language on Empathy for Pain

Klarissa Lopez, Montae Bermudez, Brandon Boring, Matthew Cline, Diya Dharmendran, Jyostna Vaid, Karina Febre, Vani Mathur; Texas A&M University

Language of Pain: The Influence of Spanish-English Bilingualism and Vignette Language on Empathy for PainKlarissa L. Lopez, Montae E. Bermudez, Brandon L. Boring, Matthew Cline, Diya Dharmendran, Karina Febre, Jyotsna Vaid, Vani A. MathurTexas A&M UniversityOver 60% of the world's population, including 76 million Americans, speaks more than one language,

yet multilingualism is underrepresented in pain research. Past research shows multilingual experiences (e.g. learning another language, exposure to a second language environment) are linked to enhanced perspective-taking and empathy, and perspective-taking interventions improve patient-physician rapport and pain equity. Therefore, we hypothesized multilingualism would enhance empathy and equitable pain assessment for Spanish- and English-speaking patients. We also investigated the effects of presentation language on empathy and pain invalidation among Spanish-speaking multilinguals. A total of 621 student volunteers (252 Spanish multilinguals, 66 non-Spanish multilinguals, and 315 English monolinguals) read a vignette describing a fellow student's pain in either Spanish or English. Results indicated that presentation language had a significant effect on empathy, but not pain invalidation, such that there was an English-favoring empathy bias among multilinguals. However, multilinguals evidenced more empathy and less pain invalidation compared to monolinguals. These results highlight language bias in empathy as a contributing factor to pain disparities, but also the potential buffering effects of multilingualism. Further, these findings begin to address the underrepresentation of multilinguals in pain research and may guide future studies toward the inclusion of language-related measures.

The Pathway From Perceived Discrimination To Pain: The Role Of Heightened Vigilance
Maya Joshi Delity, Alexandra Otto, Amy Wachholtz; University of Colorado Denver

Pain disparities reflect complex social healthcare inequities. Despite growing recognition of perceived discrimination on the pain experience, the precise pathways through which discrimination affects pain remain understudied. The present study investigated the mediating role of heightened vigilance in the relationship between perceived discrimination and pain outcomes. Data from the 2023 National Health Interview Survey was used in this report. 29,516 adults, 7,736 adults of whom had chronic pain, completed The Everyday Discrimination Scale, Heightened Vigilance Scale, and a pain frequency question. Those with chronic pain reported pain interference. A causal mediation analysis of the total sample showed a significant total effect of discrimination on pain frequency (β=0.047, <.001). There was a significant indirect effect (β = 0.0154, 95% p< .001), but a direct effect remained (β=0.0323, p<.001). Approximately 32.33% of the total effect of discrimination was explained by heightened vigilance. A second mediation analysis of individuals with chronic pain found a significant total effect of discrimination on pain interference (β=0.012, p<0.001). A significant indirect effect (β = 0.006, p<0.001), but nonsignificant direct effect (β=.005, p=NS) demonstrated full mediation of heightened vigilance between discrimination and pain interference (proportion mediated = 53.9%). In the general population, discrimination predicted increased pain frequency both directly and indirectly through heightened vigilance. In a chronic pain population, heightened vigilance fully mediated the effect of discrimination on pain interference. Findings offer a potential therapeutic target in heightened vigilance for individual-level interventions, while also demonstrating the need for collective action and systemic policy changes to reduce pain disparities.

Pain by Proxy: Vicarious Discrimination is Associated with Sensitization
Diya Dharmendran, Namrata Nanavaty Vasquez, Klarissa Lopez, Montae Bermudez, Vani Mathur; Texas A&M University

Witnessing discrimination against family, friends, or even strangers becomes a mirror reflecting, “This could be you”, amplifying stress and leading to poorer health outcomes. Despite its prevalence, vicarious discrimination is not widely understood, especially in the context of pain, where the study of discrimination has been confined to personal experiences. We explored the relationship between vicarious racialized discrimination (i.e., discrimination against one’s own racialized community and family members) and laboratory pain among 43 adults without chronic pain (21 women, 21 men, 1 gender nonconforming, 18 Black, 25 Latinx, M age = 22.4, SD = 4.79). Vicarious discrimination was reported by all participants, indicating this is a salient and prevalent experience. Greater vicarious discrimination was associated with greater length ($r = 0.321$, $p = 0.036$) and severity ($r = 0.523$, $p < .001$) of aftersensations across participants, but was not associated with pain tolerance or conditioned pain modulation. Results suggest that even vicarious discrimination may be linked to sensitization. This adds to the literature on discrimination and pain, indicating that the pain burden of racialized discrimination extends beyond those most directly targeted to impact whole families and communities. This also suggests that existing effect sizes of discrimination on pain may underestimate cumulative personal and communal effects and reinforce the imperative for societal interventions to reduce pain burden and ultimately eliminate pain disparities.

Predicting High Impact Chronic Pain Diagnosis Using Psychological and Sociocultural Patient Characteristics

Troy C. Dildine, Titilola Falasinnu, Natacha Telusca, James Kahn, Beth Darnall, Sean Mackey; Stanford University School of Medicine

More than 10 million Americans have high impact chronic pain (HICP), a condition marked by 1) severe and widespread pain, 2) debilitating impacts on social, work, and self-care activities and 3) high healthcare utilization. Although HICP has effective social and psychologically based treatment targets, with little previous research, HICP is often overtreated with problematic medications. HICP is also marked with heterogenous occurrence and patient profiles, further increasing the need for the creation and use of predictive models to better classify HICP and identify its potential risk factors and treatment targets. Here, we assessed data from the Stanford Pain Management Center using our open-source learning health system, CHOIR, to identify social and psychological targets for HICP using machine learning approaches and a health equity lens. We examined data from >75,000 clinical visits across 17,354 patients (67.6% White; 75.1% Female). Using the GLMNet package in R with a cross validation 70/30 train/test split we assessed how 18-social and PROMIS-based measures associated with HICP classification (Pain Interference T-score >= 65). We compared lasso, ridge, and elastic net models and observed the greatest model influence from satisfaction of social roles, pain catastrophizing, depression, and physical function. Furthermore, we note high AUC across our models (0.85-0.86), accuracy of classification was moderately successful (Macc: 0.68), and no differences in model performance emerged by sociodemographic features. These findings highlight the importance of targeting social and psychological factors in the management and identification of HICP and underscore the potential of machine learning approaches to inform equitable treatment strategies.

Race/Ethnicity Moderates The Relationship Between Pain-Related Injustice And Anticipatory Appraisals Of Pain And Anxiety Among Individuals With Chronic Low Back Pain

Mark Vorensky, John A. Sturgeon, Adam Guck, Zina Trost; Rutgers University

Evidence suggests individuals with chronic low back pain (CLBP) who identify as Hispanic or non-Hispanic Black (NHB) have greater anticipatory appraisals of pain and anxiety before functional everyday activities than non-Hispanic White (NHW) peers. Previous studies have found a unique role for injustice appraisals in predicting pain and disability among individuals with CLBP who identify as Hispanic and NHB. This study examined pain-related injustice as a potential mechanism underlying these racial/ethnic differences. Participants (n=138; Hispanic=43, NHB=44, NHW=51) with CLBP for at least 3 months completed the Injustice Experience Questionnaire (IEQ). Anticipatory appraisals of pain and anxiety were assessed using a 100-point visual analogue scale before performing a bed task (lying down/getting up) and chair task (sitting/standing). Moderation analyses using Hayes PROCESS Macro Model 1 tested IEQ score as the independent variable, anticipatory appraisals as dependent variables, and race/ethnicity as the moderator. IEQ scores were positively correlated with anticipatory appraisals ($r=0.47$ for all associations, $p<0.001$). Race/ethnicity moderated relationships between IEQ scores and anticipatory appraisals of pain before the bed task ($p=0.01$) and anxiety before the bed ($p=0.03$) and chair ($p=0.005$) tasks. Stronger associations between IEQ scores and anticipatory appraisals of pain and anxiety were observed among Hispanic and NHB participants compared to NHW participants. These findings highlight racial/ethnic differences in how pain-related injustice relates to anticipatory appraisals of pain and anxiety, emphasizing the importance of tailored interventions when addressing inequities in CLBP. Funding: K12NS130673.

Examining Sociocultural Stressors and Resilience Factors for Latinx Youth with Chronic Pain

Theresa Kapke, Susan Tran, Kevin Berridge, Myah Kannout, Rebekah Sheih, Paulina Paredes Cienega, Elizabeth Fenelon, Brynn LiaBraaten, Steven Weisman, Keri Hainsworth; Medical College of Wisconsin

Latinx youth represent the largest and fastest growing ethnic minority group in the United States (Jones et al., 2021). Latinx youth are known to experience significant barriers to accessing pain management services, receive sub-optimal care, and are likely to have negative healthcare experiences (Morales et al., 2021; Nguyen et al., 2005). We conducted an in-depth qualitative assessment to better understand their lived experience in order to address existing disparities and improve care. Research participants included 10 Latinx youth presenting to a multidisciplinary pediatric chronic pain clinic (mean age = 15.5, SD = 2.01; 70% female). Semi-structured interviews were conducted in English or Spanish, and were focused on the lived experience of pain, as well as barriers to and facilitators of care. Guided by thematic analysis (Braun & Clark, 2006), qualitative data analysis was conducted using NVivo 15. Results suggested that the majority of participants reported sociocultural stressors. Specific themes included stress related to 1) relationships with same-aged peers; 2) academics; 3) life changes; 4) family conflict and

responsibilities; 5) experiences of racism and discrimination; 6) ethnic identity isolation; and 7) cultural intragroup conflict and standards. The extent to which sociocultural stress affected pain varied, but many youth reported that stress worsens pain. Resilience factors contributing to lower stress included: 1) shared cultural values and beliefs; 2) respect; 3) effective communication, and 4) social support. Latinx youth with chronic pain report various sociocultural stressors and resilience factors that may affect their lived experience of pain.

Exploring Pain Coping Strategies Among Emerging Adults: The Role of Race and Discrimination

Kayla McCracken, Elizabeth Fenelon, Keely Bieniak, Paulina Paredes Cienega, Susan Tran; DePaul University

Little is known about how the coping strategies that emerging adults (EAs) with pain use across racial groups. This study aims to address the gap by examining similarities and differences in coping strategies and possible relationship to experienced discrimination. Undergraduate students in psychology courses with pain (N = 383) completed self-report measures assessing pain, coping strategies, and discrimination. The most used coping strategies for all EAs were distraction (M = 6.14), acceptance (M = 5.56), and planning (M = 5.41). White/European Americans reported significantly higher substance use (M = 3.59) compared to Asian Americans (M = 2.57; F (4, 378)= 3.886, p = .004) . African Americans (M = 4.69), Latinx (M = 4.21), and Asian Americans (M = 4.27) reported higher use of religious coping compared to White/European Americans (M = 3.22; F(4, 378) = 6.716, p < .001). Discrimination was associated with denial (r = .471, p = .011) and behavioral coping (r = .553, p = .002) among African Americans; denial (r = .43, p < .001), venting (r = .394, p < .001), humor (r = .322, p = .002), and self-blame (r = .299, p = .004) among Latinx. EAs with pain had more similarities than differences across racial groups, distraction and acceptance were used frequently. Racial background influenced both substance use and religious coping behaviors. Individual differences including race and experiences with discrimination should be considered when developing pain coping interventions.

Reducing Pain Care Disparities: Insights from Physicians' Reactions to a Virtual Perspective-Taking Intervention

Kristina Bogdan, Alexis Grant, Tracy Anastas, Adam Hirsh; Indiana University-Indianapolis

We qualitatively analyzed physicians' written reactions to a novel virtual perspective-taking intervention to reduce race and socioeconomic disparities in pain care. At baseline, physicians made pain treatment decisions for 12 virtual patients (VPs) with chronic pain that varied by race (Black/White) and socioeconomic status (High/Low). Physicians who demonstrated treatment bias were randomized to a control group or a perspective-taking intervention where they (a) received feedback about their bias and (b) interacted with two VPs who were conversationally fluent in conveying how pain has impacted their daily lived experiences (e.g., family, work, recreation). Upon completion, physicians were prompted (open-text field) for their reactions to receiving feedback and interacting with the VPs. Approximately 92% of physicians in the

intervention group responded (46.4% female, 66.7% White, mean age = 29.8 years). Two experienced coders individually reviewed the responses three times, meeting to discuss emergent and recurrent themes and to revise codes between each pass. Separate codebooks were used for reactions to bias feedback (n=81) and VP interactions (n=83). Seven themes emerged for bias feedback; the most common were Sparked New Insight/Surprising (n=43; e.g., "helpful and enlightening"), Generally Positive (n=22), and Defensive/Skeptical (n=22). Ten themes emerged for VP interactions; the most common were Technology (n=26; e.g., "little choppy," "well-designed"), Clinical Relevance (n=24), and Realism (n=23). These qualitative findings are promising and complement the quantitative findings demonstrating the intervention's efficacy. Collectively, they underscore the need to carefully consider clinician acceptance of bias interventions to ensure their successful implementation in clinical practice. Funding: NIH (R01MD008931).

Predicting Prospective Chronic Pain Onset At The 5-year Follow Up In The Oklahoma Study Of Native American Pain Risk

Aleiyah Fields, Jamie Rhudy, Parker Kell, Brandon Jones, Taylor Brown, Hayden Ventresca, Claudia Vore, Kayla Trevino, Joanna Shadlow, Travis Lowe; The University of Tulsa

Native Americans (NAs) experience a significant chronic pain inequity compared to non-Hispanic Whites (NHWs). To evaluate this inequity, the Oklahoma Study of Native American Pain Risk (OK-SNAP) recruited healthy, pain-free NAs and NHWs for two laboratory visits and assessed mechanisms consistent with the biopsychosocial model of pain: demographics, physical variables, psychosocial factors, and nociceptive/pain phenotypes. Participants were then surveyed every six months to assess for chronic pain onset. Prior findings at a 2-year follow-up showed that NAs were almost three times more likely to develop chronic pain than NHWs. Moreover, psychosocial factors (discrimination, stress, pain-related anxiety), cardiometabolic load (higher body mass index and blood pressure, lower heart rate variability), and impaired inhibition of spinal nociception partly mediated the pain inequity. Further investigation is needed to see if this pain inequity is stable over time and whether biopsychosocial variables still mediate the inequity. To address this, the current study examined data from the 5-year follow-up. Results found that the inequity worsened. NAs were 4x more likely to develop chronic pain than NHWs (OR = 4.025; CI=1.966, 8.239). Analyses also replicated prior mediation results (psychosocial and cardiometabolic factors were linked to chronic pain onset) but also found two new pathways: one linking discrimination, stress, sleep problems, and pain amplification to increased pain risk, and another linking discrimination to higher spinal nociceptive thresholds and pain risk. These findings provide further evidence for a NA pain inequity and identify multiple psychosocial, cardiometabolic, and nociceptive targets for primary interventions.

Preliminary Pain Profiles In Children With Cerebral Palsy Undergoing Lower Extremity And Spinal Fusion Surgery

Chantel Burkitt, Elizabeth Boyer, Kyle Nickodem, Jason Howard, Wade Shrader, Tom Novacheck, Frank Symons; Gillette Children's Hospital

Orthopedic surgeries are exceedingly common in individuals with cerebral palsy (CP), yet little

is known about the associated pain experience. The aim of this study was to quantify the trajectory of pain intensity and interference in the six months after surgery in children with CP and determine whether distinct pain profiles emerged. A prospective sample of 101 children with CP undergoing orthopedic surgery between the ages of 5.6-18.0 years (mean 11.5 years, 49% ambulatory, 65% male) was enrolled. Surgery types included spinal fusion (n=14), single-event multilevel surgery (n=61), foot reconstruction (n=7), and others (n=19). Latent profile analysis was used to examine preliminary pain intensity and pain interference trajectories at 1, 3, and 6-months after surgery. Numeric Rating Scale of pain intensity and Brief Pain Inventory pain interference items were completed by parents. Two distinct pain intensity profiles emerged with high entropy (.90). Most children (n=91) were in Trajectory 1 (T1) with mild pain after surgery with complete resolution by six months. Children in T2 (n=10) had moderate pain after surgery with incomplete resolution. Three distinct pain interference profiles emerged with high entropy (.94). Most children were in T1 (n=79) or T2 (n=17) with mild or moderate pain after surgery, respectively, followed by complete resolution by six months. Children in T3 (n=5) had severe pain interference after surgery with incomplete resolution. This is the first study to identify distinct surgical pain profiles in children with CP. Next steps include identifying risk factors predictive of incomplete pain resolution after surgery. Funding: R01HD108406.

Understanding Pain Communication for Black Patients with Advanced Lung Cancer: A Pilot Study

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Black patients with advanced lung cancer (LC) experience more pain than White patients. Poor pain communication may contribute to LC pain inequities, yet pain communication between Black patients with LC and their clinicians is not well-characterized. We conducted a secondary analysis of a multi-method, longitudinal, observational study examining routine visit communication between self-identified Black patients with advanced LC (n=20) and non-Black oncologists. Patients reported their symptom communication satisfaction immediately after their visit, and we coded Shared Decision Making (SDM; OPTION-5) scores for pain discussions from visit audio-recordings. Patients reported pain at their visit (ESAS; 0 “no pain” to 10 “worst possible pain”) and one month post-visit (FACT-G7; 0 “not at all” to 4 “very much”). Descriptive statistics characterized pain SDM, and two-sided correlations examined how coded SDM and symptom communication satisfaction related to patients’ pain. Half (n=10; 50%) of patients reported pain at their visit, and pain was discussed in 60% (n=12) of visits. Pain was raised equally by clinicians (n=6; 50%) and patients/caregivers (n=6; 50%). SDM scores range from 0-100, however pain communication received low SDM ratings (M=2.70, SD=4.45, range 0-15) with half (n=6) receiving a 0 score. Patient-reported symptom communication satisfaction was significantly associated with lower pain one month later ($r = -.49$, $p = .014$), though coded pain SDM was not significant ($r= -.38$, $p=.235$). Our findings highlight the need for research in pain communication for Black patients with LC, including developing pain communication quality assessment methods for this population with community feedback.

The Role of Culture in Shaping Affective Responses to Physical Pain: Clinical Insights and Future Research Opportunities

Marie-Pier Plouffe-Demers, Stéphanie Cormier, Camille Saumure, Daniel Fiset, Caroline Blais; University of Quebec in Montreal

This systematic review, conducted in accordance with PRISMA guidelines, provides a comprehensive overview of current knowledge on how cultural environments shape pain communication. The review examines each stage of the pain communication process—from the origin of pain to its expression—including conceptualization, experience, regulation, and expressivity. From an initial pool of approximately 700 articles, 59 studies were selected for detailed analysis and quality assessment. To facilitate interpretation, the review classified cultural groups examined in these studies according to Schwartz's seven transnational cultural groupings (2004; i.e. West Euro, East Euro, English-speaking, Latin American, South Asian, Confucian and sub-Saharan African nations) with an additional category for Middle Eastern nations, as per Gupta and Hanges (2004). The findings reveal significant gaps in the literature, notably the absence of standardized tools for assessing the affective dimension of pain across cultures, with nearly 40 different instruments identified. Furthermore, the heavy reliance on self-reported measures, primarily questionnaires, which were developed in specific language and culture complicates the identification of genuine cultural differences. The review also highlights an underrepresentation of certain world regions, particularly Sub-Saharan Africa and Latin America. Based on these insights, recommendations were developed and will be reviewed by a panel of expert clinicians and researchers using the Delphi method. This structured communication technique facilitates consensus-building among experts on complex topics. In conclusion, this review underscores the need for a systematic, culturally sensitive approach to pain communication research to improve validity and inform clinical practices that reflect diverse cultural contexts.

Feasibility Of A Chronic Pain 101 Workshop For Community Health Workers In A Federally Qualified Health Center

Mary Janevic, Jennifer Hopson, Lisa Rutledge, Rebecca Lindsay, Nikita Mukkamala; University of Michigan School of Public Health

Federally Qualified Health Centers (FQHCs) provide health care to low-income, often minoritized patients who are disproportionately affected by chronic pain. Many FQHCs employ Community Health Workers (CHWs) to provide nonclinical services including culturally congruent health education and addressing social determinants of health. In a collaboration with a Detroit-area FQHC, we developed a 1-hour in-person workshop to teach CHWs working across diverse content areas (e.g., diabetes care, HIV prevention) basic information about chronic pain that could inform their interactions with patients. The workshop was co-delivered by researchers and CHWs with experience in delivering a pain self-management intervention. Content included how pain works, self-management strategies, and insights from the CHWs. The evaluation of this novel training focused on feasibility as indicated by attendance and satisfaction, and a pre-post knowledge quiz. Nine CHWs (of 12 invited) attended. The mean pre-test score was 4.7 out of 5 true/false items, and 4.8 at post-test. All attendees agreed that the workshop increased their

understanding of pain management techniques, and that they felt more confident talking with patients about pain management. All but one agreed that the workshop increased understanding of how pain works in the body and brain. Open-ended comments were uniformly positive. Results show that a brief pain workshop for CHWs is feasible and well-received. Learnings can inform the future development of a chronic pain "microcredential" for CHWs that will promote pain equity by equipping CHWs - who serve some of the nation's most vulnerable populations - with skills in supporting effective chronic pain self-management.

Sleep Disturbance, Pain Catastrophizing, and Perceived Burdensomeness Among Native Americans with Chronic Pain

Taylor Brown, Cassandra Sturycz-Taylor, Tyler Toledo, Erin Street, Joanna Shadlow, Jamie Rhudy; TSET Health Promotion Research Center

Native Americans (NAs) have the highest rates of chronic pain and suicide among all U.S. racial/ethnic groups, yet research on the links between chronic pain and suicide risk in NAs is limited. The interpersonal theory of suicide proposes that suicidal ideation emerges when individuals experience high levels of perceived burdensomeness (PB). Non-NA research finds that sleep disturbance is associated with increased pain catastrophizing (PC) and PB, but evidence on which facets of PC, i.e., helplessness, magnification, or rumination, are linked to sleep disturbance and PB is mixed and has not been explored in NAs. This study examines whether PC facets mediate the relationship between sleep disturbance and PB in 113 NAs with chronic pain (68% female; Mage=50.48, SDage=16.74; Mpain=6.38, SDpain=2.51). Sleep disturbance was assessed from the PROMIS-Sleep Disturbance scale and pain catastrophizing facets were assessed from the Pain Catastrophizing Scale. PB was assessed from the associated subscale of the Interpersonal Needs Questionnaire-12. Results found sleep disturbance was significantly associated with higher scores on all PC facets, as well as higher PB, but only the helplessness facet was significantly associated with higher PB. Further, there was a significant indirect effect from sleep disturbance to PB via helplessness (β=.15, 95%CI=.03, .29). This suggests sleep disturbance contributes to heightened pain-related helplessness, which in turn increases feelings of PB. Interventions for NAs with chronic pain that improve sleep and reduce pain-related helplessness may be important for reducing PB thereby lowering risk of suicidal ideation.

Does Native American Cultural Connectedness Protect Against Chronic Pain Risk? Preliminary Results From The Oklahoma Study of Native American Pain Risk III (OK-SNAP III)

Brandon Jones, Parker Kell, Hayden Ventresca, Claudia Vore, Taylor Brown, Kayla Trevino, Travis Lowe, Joanna Shadlow, Jamie Rhudy; TSET Health Promotion Research Center

Native Americans (NAs) develop chronic pain at 4x the rate of non-Hispanic Whites (NHWs), an effect that is partly mediated by impaired descending inhibition of spinal nociception (DISN). Cultural connectedness (CC) is a form of NA cultural resilience that is associated with better mental and physical health. However, it is unknown whether CC provides pain resilience and reduces chronic pain risk. The present study examined this issue in 55 healthy, chronic pain free

NAs from OK-SNAP III (27% male; MAge=31.09, SD=12.55). Facets of CC were assessed from five validated scales: American Indian Enculturation Scale, Cultural Connectedness Scale, Communal Mastery Scale, NA Spirituality Scale, and the Vancouver Index of Acculturation - Heritage Subscale. Self-reported pain resilience was assessed from the Pain Resilience Scale. DISN was assessed from conditioned pain modulation of the nociceptive flexion reflex (CPM-NFR), a physiological marker of inhibition of spinal nociception. A principal component analysis was used to create a single CC latent variable that explained 55% of the variance in the five CC scales. Results from bootstrapped mediation analysis indicated the latent CC variable was significantly associated with pain resilience (β=0.47, $p<0.001$) and pain resilience was significantly associated with better CPM-NFR inhibition (β=-0.43, $p<.01$). Moreover, a significant indirect effect was found (β=-0.20, 95%CI: -0.38, -0.05) indicating pain resilience mediates a relationship between CC and CPM-NFR. These findings suggest CC buffers against NA chronic pain risk by boosting pain resilience and improving DISN.

Characterizing Barriers and Facilitators to Underrepresented Patient Engagement in a Chronic Pain Clinical Trial

Matthew DePuccio, Daniel Torrez, Elizabeth Hsu, Elizabeth Lynch, Rachel Bergmans, Robert McCarthy; Rush University Medical Center

Clinical trials are fundamental for identifying factors that predict susceptibility or resilience to the development of chronic pain after surgery. However, information about the factors that make these trials accessible or burdensome to underrepresented (e.g., racial minority) patient populations is needed to advance chronic pain research. This study aimed to promote diversity in health-related research by understanding the needs of underrepresented patient populations and clinical trial stakeholders of a multi-site observational study (A2CPS) conducted in the mid-west U.S. We interviewed underrepresented total knee arthroplasty and thoracotomy surgery patients (n=26), clinicians and non-clinical study staff (n=11), and community-based providers (n=10) regarding the barriers to and facilitators of participating in clinical trials. Interviews were recorded, transcribed, and analyzed thematically to identify related concepts and patterns within the data. Common barriers to patient participation included having little or no general knowledge of clinical trials, needing more time to participate, and distrusting research and medicine influenced by past experiences. Addressing patients' social needs (e.g., offering travel vouchers), communicating study expectations clearly, and building trust between patients, clinicians, and study staff were identified as facilitators of clinical trial participation and engagement. Clinical trials intentionally designed around the needs and preferences of patients and study stakeholders, akin to the principles of community-based participatory research, could enhance the recruitment of diverse patient populations in chronic pain studies by overcoming distrust between patients and medical centers and leveraging existing partnerships with community-based organizations to target and address patients' unmet needs shown to impede participation. Funding: NIH (3U24NS112873-04S3).

Advancing Equity In Lupus Chronic Pain Through A Yoga-Based Intervention

Rachel Bergmans, J. Michelle Kahlenberg, Dominique Kinnett-Hopkins; University of Michigan

Chronic pain disproportionately affects Black women with systemic lupus erythematosus (SLE), representing a critical need for equitable solutions. Despite effective treatment of SLE disease activity, many individuals have debilitating chronic pain that is inadequately treated with steroids and opioid medications, which carry significant risks with long-term use. Integrative treatment modalities, like yoga, can alleviate chronic pain in other chronic inflammatory conditions, but evidence supporting their consideration for SLE chronic pain remains elusive. To address this gap, we developed a multicomponent, person-centered, and yoga-based coaching program for SLE chronic pain, called MiPAL, that draws from motivational interviewing principles and social cognitive theory. Instead of assigning a regimented yoga practice, MiPAL is tailored based individual preferences and limitations with the support of a health coach who encourages participants to take ownership of their goals for behavior change. As an interdisciplinary team of researchers, clinicians, and people who have lived experience with SLE, we are focused on the need for safer, more effective, and more equitable SLE pain management. When designing MiPAL, we prioritized Black perspectives to overcome inequities in SLE care and research conduct. This study aims to 1) determine MiPAL's feasibility using a pragmatic trial (n=15) and 2) increase MiPAL's acceptability and accessibility among Black women through a community-engaged approach that includes focus groups and qualitative interviews. Our findings will inform the broader field of pain science on the value of community-engaged and person-centered interventions for advancing equity in pain care. We expect preliminary data for dissemination by April 2025.

Pain Interference and Insomnia Symptoms Help Mediate the Relationship Between HIV-Status and Substance Use: A Chronic Pain Perspective

Joanna Hobson, Shannon Gilstrap, Dyan White-Gilliam, Shameka Cody, Robert Sorge, Justin Thomas, Burel Goodin; University of Florida

People living with HIV (PLWH) often suffer from chronic pain due to a variety of reasons (e.g., poor sleep, mental health, neuropathy). These conditions are associated with decreased retention in care, nonadherence to antiretroviral therapy, disability, and self-treatment for pain. As pain interferes with quality of life, PLWH develop sleep conditions, with insomnia being the most prevalent. The undertreatment for pain in minority populations often results in substance use as a coping mechanism. Illicit substance use has become a major public health concern for the HIV and pain treatment spectrum, acting as a catalyst for the development of further morbidities and mortality. The purpose of this study was to elucidate whether pain interference and insomnia symptoms served as mediators in the relationship between HIV-status and current illicit substance use. Seventy people with mild to severe pain were recruited from near UAB's campus and completed questionnaires as well as a urine drug screener. 41 participants were HIV+ (58.6%), and 56 participants (80%) had a diagnosis of chronic pain. This sample was predominantly Black (77.1%) women (57.1%), and below the poverty line (75.9%). HIV+ individuals experienced greater insomnia symptoms ($p = .027$), pain interference ($p < .001$) and illicit substance use ($p = .015$) than HIV- individuals. There was an indirect effect of HIV-status on illicit substance use via pain interference and insomnia symptoms with a point estimate of .080, 95% BCI (.008 - .211). These findings highlight the need for holistic interventions to manage pain in PLWH, minimizing illicit substance use.

Interrater Agreement Between a Large Language Model and Human Raters for Pain Psychotherapy Fidelity Assessments
Zan Wynia, Maya Delity, Lauren Morris, Kathryn Costello, Yoni Ashar; University of Colorado

Psychotherapy for pain is a growing field. Treatment fidelity assessment is critical but resource intensive. Large language models (LLMs) could potentially reduce this burden. We studied how well an LLM rates treatment fidelity compared to human raters for Pain Reprocessing Therapy (PRT) and Cognitive Behavioral Therapy (CBT). This study was conducted at the University of Colorado - Anschutz Medical Campus using recordings from an ongoing clinical trial comparing PRT vs. CBT for chronic back pain. Three human raters were compared to Claude-3-Opus. Humans watched session recordings while Claude analyzed de-identified auto-generated Zoom transcripts. One rater (KC) served as the gold standard. Twelve features each for PRT and CBT were assessed across 20 PRT and 13 CBT sessions. A prevalence and bias adjusted kappa (PABAK) was calculated for each feature. Comparing Claude to KC, average PABAKs were 0.27 and 0.59 for PRT and CBT features respectively. Comparing Claude to non-gold standard raters showed average PABAKs of 0.27 for PRT and 0.75 for CBT features. Full analyses will be completed by January, 2025. This study found moderate to high LLM-human agreement for CBT features but not PRT features. This suggests LLMs may better assess fidelity for manualized therapies like CBT. PRT is comparatively less manualized and contains fidelity features an LLM may struggle to identify. Limitations include the small sample size and potential Zoom transcript errors.

Other

The Development Of Education Materials For Patients Dealing With Chronic Pain With Modules On The Anatomy, Physiology And Psychology Of Pain And Patient Selected Topics
Erika Manning, Robert Decidue, Colin Bruce, Emily Cheng; Thomas Jefferson University

Studies have demonstrated neurophysiologically based education (Ferrell at al 1993; Van Oosterwijck et al 2013; Lee et al 2016; Kohns et al 2020; Luis Suso-Marti et al 2022) and psychoeducation (Jerjes et al 2007; Luciano et al 2011) can lead to beneficial results in patients dealing with chronic pain, including reduction of pain ratings, less medication usage, and improved quality of life. The current project focused on the development of an education course, including brief (15-20 minute) modules on the anatomy, physiology, and psychology of pain. The program also includes targeted lectures on issues identified by chronic pain patients. Fifty chronic pain patients were recruited through social media and were asked to view components of 20 brief lectures in the program. The majority (72%) of the patients indicated satisfaction with the programs and reported that they felt the information included in the program could help them to better cope with their pain. Almost 90% of the patients reported that rather than an overall course curriculum or course, modules should be created as independent educational/self-contained programs, so patients can focus on areas of personal interest. Finally, pain patients asked for a focus on the development of educational materials geared at their family and loved ones, to better help them understand the issues associated with living with chronic pain. These

preliminary results indicate that this educational program would be well-received by patients, especially if modules are created to address specific topics and issues, rather than being part of a more integrated curriculum.

Experimental Pain Sensitivity and Frequent Tooth Pain
Hong Chen, Mengda Yu, Jolynn Pek; The Ohio State University

This study evaluated the relationship between experimental pain sensitivity and the self-reported frequency of toothache. Secondary data were analyzed using the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) baseline dataset. Self-reported frequency of toothache was categorized into “frequent” (every month or more) and “non-frequent” (otherwise). Experimental pain sensitivity measures included pressure pain thresholds (PPT) in 3 facial and 2 non-facial sites, mechanic cutaneous pain threshold (MCP), heat pain threshold (HPTh), and heat pain tolerance (HPTo). Descriptive statistics were summarized by toothache groups using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Characteristics were compared by toothache groups using t-test and Chi-square tests. Multivariate analysis using logistic regression was conducted to evaluate the relationship between each pain sensitivity measure and the presence of frequent toothache, adjusted for demographics and study site (α=0.05). All analyses were conducted using SAS (version 9.4). Overall, 3240 individuals were included in this analysis. The mean age was 27±7.8 years. Frequent toothache was reported by 243 (7.5%) participants. Those reporting frequent toothache were older (mean age 28.1 vs. 26.9, p=0.02) and predominantly African Americans (54.7%, p<0.0001). Multivariate analysis showed that mean pressure pain thresholds were lower at temporomandibular joint (170.9 vs. 182.2), trapezius muscle (312.4 vs. 331.9), and lateral epicondyle (156.3 vs. 166.2) in those with and without frequent toothache (p’s <0.05). No group differences were found for MCP, HPTh and HPTo. Further research is needed to understand the pathophysiology of frequent toothache in demographically specific groups.

Unveiling The Hidden Construct in Assessing Pain Catastrophizing
Omid Khoshavi, Adam J. Janowski, Laura A. Frey Law; Carver College of Medicine

The Pain Catastrophizing Scale (PCS) measures exaggerated negative thoughts and feelings about pain, asking respondents to consider, “when in pain.” However, PCS variability may result from choice of recalled pain condition(s), which is typically not assessed. Thus, the purpose of this study was to investigate the pain characteristics individuals consider when completing the PCS and their association to PCS scores. 89 adults (27±6 years; 29% reported chronic pain) completed the PCS along with additional questions regarding the pain conditions they considered: number (1, 2, 3, 4+), intensity (0-10), and duration (acute vs chronic, single vs. episodic). Results were assessed using descriptive statistics, correlation coefficients, Chi-square, and univariate analyses. Most respondents (41%) considered 2 pain conditions, with 1 (22%), 3 (26%) and 4 (11%) also represented. Using the 1st, PCS scores increased with pain intensity ($r = 0.23$, $p = 0.03$), and varied across pain durations ($p=0.04$, $\eta^2=0.12$). Further, PCS increased with

average pain intensity for those reporting 2+ pain conditions ($r=0.40$, $p<0.001$). PCS scores did not differ by number of pain conditions ($p = 0.85$) or between those with and without a history of chronic pain ($p = 0.42$). However, those with chronic pain were more likely to recall chronic pain than those without ($p<0.001$). This study highlights that individuals consider different pain situations when competing the PCS, likely influencing scores. This suggests that when assessing pain catastrophizing, choice of referent pain condition is a 2nd unmeasured construct that may be important to consider for optimal interpretation.

Anti-PD-1 Treatment Prevents Chronic Postsurgical Pain In Mice

Mohamad Karaky, Anahita Oveisi, Lucas Vasconcelos Lima, Sahel Jahangiri Esfahani, Jeffrey Mogil, Joseph Mathew, Luda Diatchenko; McGill University

Chronic postsurgical pain (CPSP), lasting over three months after surgery, affects 5% to 85% of patients depending on the type of surgery. Previous research from our laboratories indicates that activated neutrophils prevent dexamethasone (DEXA)-induced pain prolongation after inflammatory injury. In search of the drugs that would stimulate neutrophils, we focused on so-called checkpoint inhibitors, a class of immunotherapeutic drugs that are used for the treatment of cancer. Anti-PD-1 drugs block PD-1/PD-L1 interactions between T cells and tumor cells, as well as other antigen-presenting cells (APCs), including neutrophils. Since PD-1/PD-L1 interactions lead to T cell and neutrophil inactivation, we hypothesized that anti-PD-1 treatment may prevent CPSP. To test this hypothesis, we employed CD-1 mice that underwent hind paw plantar incision and were treated with 0.5 mg/kg/day DEXA or saline intraperitoneally (i.p.) from one day before surgery until five days post-surgery. Anti-PD-1 antibody or isotype control (rat IgG2b) was administered i.p. on days 2 and 4 post-surgery (10 mg/kg each dose). A separate group received only one dose on day 2. Mechanical withdrawal thresholds were measured pre-surgery and at multiple time points post-injury. We observed that saline-treated mice recovered within two weeks, while DEXA-treated mice exhibited long lasting pain for more than 10 weeks. Anti-PD-1 treatment, either one or two doses, prevented DEXA-induced prolonged pain, with recovery within two weeks. These findings suggest that anti-PD-1 therapy may prevent CPSP, potentially through neutrophil activation, offering a novel therapeutic approach for CPSP.

Association Between Cannabis Use And Insomnia Symptoms Among Patients Prescribed Long-Term Opioid Therapy

Daniel Schriemer, Jonathan Elliott, Meike Niederhausen, Hannah Flegal, Natassja Pal, Travis Lovejoy, Steven Dobscha, Benjamin Morasco; Veterans Affairs Portland Health Care System

It is well-established that insomnia and chronic pain co-occur at high rates, with the presence of each condition negatively impacting the other. Individuals who use cannabis also report increased pain and sleep impairment relative to those who do not use cannabis. Cannabis use among patients prescribed long-term opioid therapy is common, with estimates as high as 20-40%. However, further research is needed to understand the extent to which cannabis use characteristics (frequency, total consumption) are associated with sleep functioning among individuals with pain. We examined the prevalence and intensity of insomnia symptoms among a

national sample of 405 patients prescribed long-term opioid therapy for chronic pain who reported current cannabis use and had a positive urine drug screen for cannabis. Participants were grouped by sleep quality: no insomnia (29%), mild insomnia (35%), and moderate/severe insomnia (36%). Information was collected about cannabis use frequency (based on self-report) and quantity (measured with nail samples to determine concentrations of Carboxy-THC (pg/mg)). In a multiple linear regression model controlling for demographic and clinical factors, pain interference, depression symptom severity, and PTSD diagnosis were positively associated with insomnia severity. Cannabis use quantity was not significantly associated with insomnia severity in the multivariate model. These findings suggest that, in a sample of participants who all use cannabis, the quantity of cannabis use was not significantly associated with insomnia symptoms. Future research should examine a possible threshold effect of cannabis dose on insomnia symptoms.

Quantitative Understanding of Advanced Novel Techniques for Imaging Fasciitis and Yielding a biosignature (QUANTIFY): Protocol for a cross-sectional study

Zahra Amerian, Timothy Fleagle, Utsav Tuladhar, Barbara Van Gorp, Jessica Danielson, Mederic Hall, Brian Smith, Michael Richards, Jim Holmes, Kathleen Sluka, Ruth Chimenti; University of Iowa

Myofascial pain remains an underdiagnosed contributor to musculoskeletal pain conditions, including plantar fasciitis, the most common source of plantar foot pain. The current standard for diagnosing myofascial pain is a clinical exam using manual palpation. Yet this diagnostic standard lacks objective, quantitative thresholds to more precisely assess myofascial pain, highlighting the need for validated biomarkers. This study aims to develop a diagnostic imaging biosignature, which uses both advanced MRI and ultrasound imaging techniques, to detect abnormal myofascial tissue in individuals with plantar fasciitis. The study will also explore if the diagnostic accuracy is enhanced by creating a composite biosignature that includes psychosocial factors. In this cross-sectional study, 100 participants will be recruited, including individuals with plantar fasciitis (n=50), insertional Achilles tendinopathy (n=25), and pain-free controls (n=25). Participants will undergo a clinical exam of 5 muscles in the lower leg and foot to identify sites of abnormal myofascial tissues. Pain intensity will be assessed during walking using the numeric pain rating scale (0 to 10). The primary imaging outcomes will capture the biochemical (T1ρ of muscle and fascia), biomechanical (elastic modulus of the muscle, shear strain of the plantar fascia during passive movement), and structural (fat fraction of the muscle, thickness of the plantar fascia) profile of abnormal myofascial tissue. Secondary outcomes will assess psychological factors (fear of movement, depression, anxiety). This study will provide novel mechanistic insights into myofascial pain through advanced imaging techniques, offering a biopsychosocial framework for better diagnosis and treatment of plantar fasciitis and related conditions.

Role Of Protease Inhibitor 16 In Attenuating Paclitaxel-Induced Neuropathic Pain

Md Areeful Haque, Rachelle Garrity, James M Nichols, Hoang Vu T Pham, Ronnie Trinh, Annemieke Kavelaars, Cobi Heijnen, Andrew Shepherd; University of Texas MD Anderson Cancer Center

Chemotherapy-induced peripheral neuropathy is a common, dose-limiting side effect of paclitaxel (PTX), causing pain, numbness, and tingling in 60-70% of cancer patients, but effective treatments are lacking. This study investigates the role of protease inhibitor 16 (Pi16) in attenuating PTX-induced neuropathic pain (PINP). The results show no significant differences in PTX-induced mechanical allodynia between wild-type (WT) and Pi16 knockout (Pi16-/-) mice until day 7 post-PTX injection in von-Frey analysis. While allodynia persisted for ≥8 weeks in WT mice, Pi16-/- mice began recovering by day 9 and returned to pre-injection sensitivity by day 17, suggesting that Pi16 deletion protects against persistent mechanical allodynia. Further immunohistochemistry analysis revealed increased density of CD206+ macrophages in the hindpaw skin, sciatic nerve, and dorsal root ganglia of Pi16-/- mice compared to their WT counterparts. No significant differences in inflammatory markers expression (TNF-α, IL-1β, MMP-9, iNOS, Arg-1, MRC1, IL-4, IL-10) were observed in untreated Pi16-/- bone marrow-derived macrophages (BMDMs) to WT BMDMs, although Pi16-/- fibroblasts showed increased levels of MMP-9, TNF-α, and FAP-α in RT-qPCR analysis. Notably, an upregulation of MMP-9 and chemerin and downregulation of TNF-α were seen alongside other markers in Pi16-/- fibroblasts post-PTX treatment proteome profiler array. These findings suggest that Pi16 plays a complex role in inflammation and pain resolution, and its deletion may offer protection against PTX-induced pain hypersensitivity, making Pi16 a potential target for managing PINP.

Unlocking Potential: National Institutes of Health (NIH) Helping End Long Term Addiction (HEAL) Common Data Elements (CDEs) and Data Ecosystem for Broader Research

Carolyn Conlin, Giulia Bova, Jess Mazerik, Anthony Juehne, Laura Wandner; National Institute of Neurological Disorders and Stroke

Unlocking Potential: National Institutes of Health (NIH) Helping End Long Term Addiction (HEAL) Common Data Elements (CDEs) and Data Ecosystem for Broader Research Carolyn Conlin, Giulia Bova, Jess Mazerik, Anthony Juehne, Laura Wandner; National Institute of Neurological Disorders and Stroke The Helping to End Addiction Long-term® (HEAL) Initiative is an NIH-wide effort to accelerate scientific solutions to the overdose epidemic and the crisis of pain. Two key resources within HEAL -The NIH HEAL Common Data Elements (CDE) and Data Ecosystem play critical roles in supporting this mission. The NIH HEAL CDEs provide a structured framework of validated measures to standardize data across HEAL- funded studies. This standardization not only ensures data comparability but also facilitates secondary analyses, enabling research to derive new insights and maximize the value of existing data. The HEAL Data Ecosystem serves as a centralized platform for integrating, accessing and sharing data across studies. By supporting harmonization of datasets and leveraging semantic connections, the ecosystem enhances data reuse and interoperability, driving comprehensive data harmonization. It's alignment with the CDE program facilitates data reuse and interoperability while enabling AI- readiness powered through granular metadata and big data harmonization. The poster will highlight how the broader research community can leverage the tools available within the HEAL Common Data Elements and Data Ecosystem to advance scientific discoveries, improve data quality and drive innovation across pain and addiction. In order to ultimately foster collaboration and expand the impact of HEAL resources.

Evaluation Of The Role Of Sphingosine-1-Phosphate Receptor-1 In Aromatase Inhibitor Induced Painful-Like Behavior In Mice

Sara Herz, Isis Betancourt-Toscano, Sami Ali, Caleb Tiron, Martial Caillaud, M. Imad Damaj; Virginia Commonwealth University School of Medicine

Breast cancer is the second leading cause of cancer deaths among women in the U.S., with 310,720 new cases annually. The majority of cases involve postmenopausal women with estrogen receptor-positive (ER+) tumors, treated with letrozole, an aromatase inhibitor (AI). While letrozole prevents cancer cell proliferation, many patients experience musculoskeletal painful symptoms known as aromatase inhibitor musculoskeletal syndrome (AIMSS), leading up to 50% of women to discontinue treatment early. This study aims to investigate the role of Sphingosine-1-Phosphate Receptors (S1PRs) in AIMSS using a translational mouse model. Since global S1PR1 null mice are not viable, we used conditional gene knockout (cKO) to examine a possible CNS S1PR1 contribution to letrozole-induced AIMSS. We administered chronic oral letrozole for 15 days to ovariectomized (OVX) female cKO (C57BL/6J background) mice where S1PR1 was eliminated from neurons, astrocytes and oligodendrocytes (S1pr1 loxP/loxP; Nestin-Cre) and unrecombined littermate controls (S1pr1loxP/loxP) and assessed various behavioral changes (mechanical hypersensitivity, decrease in grip strength, nesting and wheel running). We also tested two S1PR1-targeting drugs: the functional antagonist FTY720 (fingolimod) and the competitive antagonist NIBR-0213. Letrozole-induced AIMSS was largely absent in cKO mice lacking S1PR1 in CNS cell lineages. In addition, acute administration of FTY720 and NIBR-0213 reversed AIMSS-like behaviors in a dose-related manner. These results suggest that S1PR1 activation plays an important role in letrozole- induced behavioral deficits and are promising target for treating AIMSS in breast cancer patients receiving AIs.

Pain And Fatigue Trajectories Throughout One Chemotherapy Cycle And Their Associated Gene Expressions Profiles In Colorectal Cancer Patients

Weizi Wu, Xiaomei Cong, Wanli Xu; Yale School of Nursing

Patients with colorectal cancer undergoing chemotherapy often experience significant pain and fatigue, yet effective interventions remain elusive due to limited understanding of these symptoms' complex phenotypes and biological underpinnings. This study aimed to examine pain and fatigue patterns during a chemotherapy cycle and their associated gene expression profiles. A prospective longitudinal study followed 34 colorectal cancer patients at a Cancer Institute in the Northeastern US. Pain and fatigue levels were assessed at three time points using the Brief Pain Inventory Short Form and Functional Assessment of Chronic Illness Therapy-Fatigue. Blood samples were analyzed via RNA sequencing with differential expression analysis using R packages. Linear mixed-effects models were used to identify potential biomarkers. Participants averaged 58.4 years old, with most being white (97.0%) and non-Hispanic (97.1%); 44.1% were at stage III, and 26.5% were undergoing initial chemotherapy. Abdominal pain was the most frequently reported symptom. Fatigue levels significantly increased after chemotherapy compared to baseline ($P = 0.011$) and post-recovery ($P = 0.018$). The main pathway perturbations were related to inflammatory response and myeloid cell development (FDR < 5%). Notably,

upregulation of LILRA6.1 correlated with higher pain interference (β = -6.621, P = 0.010) and fatigue levels (β = -6.621, P = 0.010). These findings suggest a link between heightened pain and fatigue, immune-inflammatory responses, erythrocyte function, and specific biomarkers. Insights from this study may inform future research and guide the development of targeted therapies to alleviate pain and fatigue in colorectal cancer patients undergoing chemotherapy.

Minimally Important Difference and Responsiveness to Change of Numerical Rating Scale for Menstrual Pain Severity

Chen Chen, Jingyue Wu, Chiyoung Lee, Hyochol Brian Ahn, Juyoung Park, Kurt Kroenke; University of Arizona

Menstrual pain affects 45%-95% of reproductive-age females, impacts quality of life, and potentially increases the risk of other chronic pain conditions. Psychometrically sound measurement tools are essential for advancing research and clinical care in menstrual pain. Numerical rating scales (NRS) are widely used to assess pain severity including menstrual pain. However, there are gaps in understanding the minimally important difference (MID) and responsiveness to change of NRS in the context of menstrual pain. This study evaluated the MID and responsiveness to change of the NRS for menstrual pain severity. The study involved 100 participants aged 14-42 who were menstruating. Participants completed two surveys about 24 hours apart, measuring menstrual pain severity (worst, least, average menstrual pain in the past 24 hours, and current menstrual pain) on a 0 (no pain) to 10 (extremely severe) scale. MID were estimated using distribution-based approaches (standard error of measures and effect size) and anchor-based approaches (using symptom interference and retrospective recall of change as anchors). Responsiveness was assessed through standard response mean and receiver operator curve analysis. Triangulating different methods, the MID estimates were close to 1 point. The NRS of menstrual pain severity were responsive to pain improvement (standard response mean ranged from 0.44 to 0.61, $p<0.001$ for between-group comparisons). Area-under-the-curve estimates ranged from 0.66 to 0.70. The findings can inform the power analyses and interpretation of studies testing menstrual pain interventions. Moreover, the findings support the use of the NRS as a responsive measure in menstrual pain research.

NIH HEAL Initiative Programs and Funding Opportunities in Training and Workforce

Laura Wandner, Elizabeth Sypek, Nora Hathan, Steven Pittenger; National Institutes of Health

The National Institutes of Health (NIH) Helping to End Addiction Long-term (HEAL) Initiative is an NIH-wide effort to speed scientific solutions to the overdose epidemic and the crisis of pain. A cornerstone of the HEAL Initiative is its commitment to workforce development, supporting the training and advancement of researchers across the spectrum of pain science and at all career stages to build a robust, multidisciplinary research community equipped to tackle the challenges of pain. Through targeted programs and notices of funding opportunities (NOFOs), the HEAL Initiative fosters the growth of a diverse and innovative research workforce. These funding opportunities are available for people across the career spectrum to expand, retain, and enhance the diversity of the workforce. This poster will provide guidance to researchers on

identifying suitable HEAL workforce funding opportunities and connecting with program officials to facilitate participation in HEAL-supported workforce development programs.

Mitochondrial Uncoupler MP-201 Reduces Neuropathic Pain
Sachin Goyal, Shivali Goyal, John G Giesler, Karin Westlund High; University of New Mexico Health Sciences Center

Our studies utilize MP-201, an oral brain penetrating prodrug of mitochondrial uncoupler 2,4-dinitrophenol (DNP) eliminating free radicals. MP-201/DNP reduces mitochondrial calcium (Ca^{2+}) influx restoring calcium balance after neuronal overactivation by closing the outer mitochondrial membrane calcium uniporter to lower calcium overload mitophagy and apoptosis. In addition to immediate biophysical benefits of lowering mitochondrial membrane potential, MP-201 has shown protective benefits to induce endogenous levels of BDNF involved in neuronal repair. Pan-neuroprotective MP-201 has shown benefits in a host of clinical syndrome models rooted in mitochondrial dysfunctional, such as TBI, ALS, Parkinson's, MS, and others. We have reported mitochondrial stress with Seahorse assessments in a chronic trigeminal injury neuropathic pain model, indicated as altered oxygen consumption rate (OCR) and oxidative stress in cortical homogenates of mitochondrial fractions. New data indicate relevance of managing mitochondrial oxidative stress as a means to reduce orofacial and sciatic chronic neuropathic pain-related behaviors, cognition, anxiety and depression. MP-201 was given orally after trigeminal and sciatic nerve injury to target mitochondrial dysfunction, a hallmark of chronic pain. The data to be presented shows a striking effect using MP-201 reducing both types of chronic neuropathic pain. These data present a completely novel, non-addictive mechanism of action by specifically targeting calcium biophysics in the ~2000 mitochondria per neuron. The study advances understanding of neuropathic pain mechanisms and paves the way for use of this novel therapeutic intervention for nerve injury chronic pain including orofacial neuropathic pain often referred to as "suicide syndrome" which currently has no effective therapeutic. VA Merit Grant BX002695.

Challenges, Lessons Learned, and Recommendations from an International Delphi to Develop Overarching Core Outcome Sets for Acute, Acute to Chronic, Recurrent/Episodic, and Chronic Pain
Giulia Bova, Janelle Letzen, Adam Anicich, Judy Birch, Anthony Domenichiello, Ulrike Kaiser, Kate Nicholson, Daniela Rosenberger, Laura Wandner, Esther Pogatzki-Zahn; National Institute of Neurological Disorders and Stroke

Core outcome sets (COS) are important to compare and analyze data across studies. INTEGRATE-Pain developed COS for pain research and clinical practice, using a Delphi method. It was unique because persons with lived experience of pain (PWLE) were heavily involved as participants and advisors. Voters represented diverse nationalities and professions, and the COS were developed to encompass all pain conditions (Bova et al, 2023). Given the scale and uniqueness of this Delphi, our methodological reflections can inform future COS efforts. This abstract presents lessons learned from a Delphi to develop COS for pain. We discuss strengths, challenges, and recommendations regarding: 1) building buy-in for the COS and

engaging voters and advisory committee (AC) members; 2) identifying/selecting domains; 3) implementing the Delphi; and 4) finalizing the COS. Findings presented are based on formal feedback from Delphi participants (open-response surveys) and informal feedback (meetings with ACs and the steering committee). We recommend including people of diverse backgrounds/opinions and PWLE at all stages of the Delphi. It's also important to ensure diversity on advisory boards. Training voters, frequent communication, and providing ample opportunities for voter feedback are crucial for ensuring shared meaning for study goals and instructions. Identifying, defining, and presenting domains for voting may require modifying domains for the study purposes. Holding focus groups prior to voting is helpful to balance domains from published literature with input from Delphi stakeholders. When finalizing results, consider a final consensus meeting and the importance of disseminating to researchers, clinicians, policymakers, and PWLE advocacy organizations.

Chemokine Ligand 12 (CCL12) Mediates Post-Surgical Pain In Mice Via IL-1b Pathway
Sabrina de Souza, Sophie Laumet, Hannah Hua, Kufreobong Inyang, Joseph Folger, Geofrroy Laumet; Michigan State University

More than 200 million people undergo surgery involving skin incision each year, but clinical pain management is far from being successful. The development of novel analgesics is restricted by limited understanding of underlying mechanisms mediating surgical pain. It is evident that the immune system plays a critical role in the development of pain. However, the contribution of immune cells and their mediator in pain still needs to be explored. The purpose of this study was to determine the involvement of inflammatory molecules in surgical pain and identify novel targets for pain relief. Using cytokine/chemokine arrays in wild type mice, we identified the Chemokine Ligand 12 (CCL12) as one of the most highly upregulated chemokines in the skin after incision. ELISA showed higher levels after 24 hours and it is dependent on the depth of incision. Plantar injection of recombinant CCL12 in naïve mice induced nociception and upregulated Il1b expression, a cytokine that directly sensitizes sensory neurons. IL-1b antagonist alleviated CCL12-induced pain. Interestingly, local neutralization of CCL12 alleviated incision-induced pain hypersensitivity and reduced Il1b expression but did not affect immune cells number in the skin. Our findings suggest that CCL12 is involved in pain sensitization through IL1-b and neutralizing CCL12 improves pain. We are currently working on the mechanisms behind CCL12 x IL-1b x sensory neurons axis. Understanding how CCL12 affects pain will allow us to build large-scale research, exploiting CCL12 neutralizing antibodies as a novel and local analgesic treatment for managing peri- and post-surgical pain. Funding: NIH R01NS121259 and R01AI177305.

Exploring Nurses' Experiences and Barriers in Postoperative Pain Management and Strategies for Enhancement
Bereket Dea; Central South University

Background: Effective postoperative pain management is essential for ensuring patient recovery and satisfaction after surgical procedures. Adequate pain relief reduces discomfort, enhances recovery outcomes, and minimizes complications. Despite its importance, nurses often face challenges that hinder their ability to implement optimal pain management practices, including

inadequate resources, insufficient training, and communication barriers within healthcare teams. This study explores nurses' experiences in managing postoperative pain, identifies the specific barriers they encounter, and suggests practical strategies for enhancing pain management practices.
Methods: Qualitative study employed a descriptive phenomenological design to explore the experiences and challenges nurses face in managing postoperative pain for surgical patients in Ethiopia. Ten nursing professionals and two hospital officer were recruited through purposive sampling to provide in-depth insights. Data were collected via face-to-face, semi-structured interviews, allowing participants to share their lived experiences. Colaizzi's seven step methodological framework guided the data analysis, providing a structured approach to uncover themes and capture the essence of participants' perceptions. This framework facilitated a comprehensive understanding of the complexities surrounding postoperative pain management from the nurses' perspectives.
Results: The findings revealed six main themes: understanding of pain management principles, knowledge acquisition and training gaps, communication barriers with interdisciplinary teams, resource limitations, patient-centered care challenges, and strategies for improvement. Nurses reported feeling underprepared due to insufficient training and resources, which hindered their ability to provide effective pain relief. Additionally, communication breakdowns with other healthcare professionals further complicated pain management efforts.
Conclusions: This study underscores the critical role of nurses in postoperative pain management and reveals interconnected barriers and facilitators that shape their ability to provide effective care. Findings highlight the need for targeted interventions and support systems to enhance nurses' capacity in managing postoperative pain. Recommendations include the implementation of enhanced training programs, improved interdisciplinary communication, and more effective resource allocation. By addressing these challenges, healthcare systems can optimize pain management practices, ultimately resulting in better patient outcomes and increased satisfaction.

National Institutes of Health Pain Consortium: Description of the goals of the Pain Consortium and Funding Opportunities

Carolyn Conlin, Leah Pogorzala, Laura Wandner, Linda Porter; National Institute of Neurological Disorders and Stroke

The National Institutes of Health (NIH) Pain Consortium (PC) aims to enhance pain research and foster collaboration among researchers across the many Institutes and Centers within the NIH that address pain. One goal of the NIH PC is to reduce the siloed nature of pain research. This goal is addressed by developing a comprehensive agenda on pain research for the institutes, identifying and disseminate key research opportunities, increasing the visibility of pain research, and advancing the agenda through the public and private partnerships. Key activities of the NIH PC involve educating the institutes and centers on current pain research efforts within the individual institutes, highlighting funding opportunities, and encouraging collaborative efforts to address gaps in pain research. The NIH PC also aims to educate researchers, people with lived experience, advocacy groups, and clinicians about pain research being conducted at NIH. The NIH institutes that are members of the NIH PC have programs and funding opportunities that are available to researchers across all career stages, across a variety of settings, and multi-disciplinary teams. Attendees of USASP will be informed of current non-HEAL funding

announcements, gain more information about how to determine which institute to submit a grant to, and other resources the NIH PC can provide to the USASP community.

Pain and Aging

Chronic Pain With Intermittent Frequency Promotes Biological Adaptation In Older Rats
Kimberly Sibille, Katrina Hamilton, Thomas Foster, Ben Burkley, Christoph Seubert, Roger Fillingim, Robert Yezierski; University of Florida

Leukocyte telomere length (LTL) is a biomarker of cellular aging. Attempts to correlate telomere length with clinical measures of chronic pain have yielded inconsistent results. One possible explanation is that previous investigations were limited by linear statistical analyses. Prior rat studies assessing the relationship between chronic stress and telomere length indicate a non-linear, inverted-U, hormesis pattern. These studies included young and middle-aged rats exposed to stress for 3 to 12 months. Extending previous findings, we investigated the relationship between LTL and the sustained stress of chronic pain extending over 18-months, in an older adult rat model. Eighteen Fisher 344 Cross Brown Norway female rats, aged 9.5 months at the start of the study, received a total of 9 hind paw injections of either saline or formalin two months apart over an 18-month period. Pain and behavioral testing were completed at multiple timepoints. Brain and blood samples were collected at the conclusion of the study. Synaptophysin, corticosterone, and telomere length were analyzed. Pain testing confirmed hyperalgesia in the formalin group. Nonetheless, the formalin group showed a trend toward longer telomere length, lower corticosterone ($p>0.05$), and higher synaptophysin ($p>0.02$) compared to the saline group. The formalin injection created a chronic pain model with intermittent pain frequency. Consistent with the allostatic load conceptualization, the chronic pain stress interspersed with periods of recovery between the formalin injections appears to have promoted adaptive biological responses.

Sleep Complaints And Pain Among American Older Adults: Findings From The National Health And Aging Trends Study
Jaspreet Kaur Sodhi; Marshall University

The study aimed to examine the association of sleep complaints with any pain, upper extremity pain, and lower extremity pain among American older adults over six years of follow-up. Participants (N=5,716) were from the National Health and Aging Trends Study (2011-2015), an ongoing nationally representative sample of Medicare beneficiaries aged 65 years and older. Measures included, socio-demographics (age, gender, race/ethnicity, and education), medical conditions, and obesity (body mass index ≥ 30 Kg/m2). Sleep complaints were the independent variable, including trouble sleeping > 30 minutes, waking between sleep, and using sleep medications. Any pain, pain in the upper extremities, and pain in the lower extremities were the outcome variables. The overall prevalence of pain in this sample was 52.3 %. Participants using sleep medications had greater (OR 1.47, 95% CI 1.34-1.61), trouble sleeping (OR 1.22, 95% CI 1.13-1.31), wakes between sleep (OR 1.20, 95% CI 1.11-1.30) odds of reporting any pain over time. Participants using sleep medications had greater (OR 1.42, 95% CI 1.29-1.55), trouble

sleeping (OR 1.24, 95% CI 1.15-1.33), and wakes between sleep (OR 1.15, 95% CI 1.07-1.25) odds of reporting any upper extremity pain over time. Participants using sleep medications had greater (OR 1.36, 95% CI 1.23-1.50), trouble sleeping (OR 109, 95% CI 1.00-1.18), and wakes between sleep (OR 1.11, 95% CI 1.02-1.21) odds of reporting any lower extremity pain over time. Understanding this complex relationship is crucial for improving pain management and reducing the burden of pain in this population.

C-Fiber Damage and Sensory Abnormalities in a Tauopathy Mouse Model
Will Hauser, Vivien Csikos, Janelle Ryals, Lana Heslop, Sarah Crowards, Gentry Totta-Griese, Trent Madden, Heather Wilkins, Doug Wright; The University of Kansas Medical Center

When high-threshold C-fibers in peripheral terminals are exposed to inflammatory mediators, their response threshold lowers, increasing nociceptor sensitivity. While normal peripheral sensitization is a protective response, long-term exposure to inflammatory damage can impair daily functioning. Tauopathies, such as Progressive Supranuclear Palsy (PSP), are primarily studied in the central nervous system, but peripheral nerve damage has also been reported. Clinical and rodent model studies have identified small-fiber neuropathy, tau deposits in peripheral tissues, and altered sciatic nerve conduction velocity in tauopathies. Abnormal tau deposits trigger an inflammatory response, activating toll-like receptor (TLR4) in the CNS. However, the mechanisms of tau-mediated damage in peripheral nerves remain unclear. To address this, we hypothesize that pathological tau acts as a damage-associated molecular pattern (DAMP), causing toxicity to C-fibers via TLR4/NFκB signaling pathways. We investigated potential C-fiber damage in tauopathies using the PS19 mouse model, which harbors a P301S tau mutation leading to overexpression of the 4-repeat tau isoform. Preliminary findings indicate thermal hypersensitivity in PS19 mice starting at three months, a decline in spatial memory at five months, and reduced intraepidermal nerve fiber (IENF) density compared to wildtype controls. Additionally, sensory nerve conduction velocity shows non-significant differences between PS19 and wildtype mice, suggesting C-fiber-specific damage. Ongoing studies focus on the role of sterile alpha and TIR motif containing 1 (SARM1) and its interaction with tau in peripheral pain pathways, examining tau's impact on peripheral tissue, pain behavior, and underlying signaling mechanisms. This study aims to explore C-fiber damage and tau-mediated signaling in tauopathies.

Exploring the Links Between Chronic Pain, Stress, and Biological Aging: A Mediation Analysis
Kiari Kinnie Davis, Khalid Freij, Tammie Quinn, Demario Overstreet, Shivraj Grewal, Fiona Agbor, Burel Goodin, Robert Sorge, Edwin Aroke; University of Alabama at Birmingham

Chronic low back pain (CLBP) and stress share major conceptual and physiological overlaps. For instance, psychological stress and CLBP persistence have been linked to biological age acceleration, as measured using DNA methylation clocks. This study investigated how perceived stress, and the pace of biological aging are associated with CLBP disability and functional outcomes. Participants (41.0 ± 15.09 years) with low-impact pain (n = 56), high-impact pain (n = 77), and no pain (n = 74) completed the Perceived Stress Scale (PSS), Oswestry Disability Index

(ODI), and the Short Physical Performance Battery assessments. We used Illumina's MethylationEPIC to determine DNA methylation and the DunedinPACE algorithm to estimate the pace of biological aging. Hayes' model 4 was used for mediation analysis, controlling for chronological age, sex, race, and BMI. Perceived stress significantly correlated with disability ($r = 0.371$) and functional performance ($r = -0.229$), but not DunedinPACE ($r = 0.111$) at $p < 0.05$. Mediation analysis revealed a significant indirect effect of perceived stress on disability through DunedinPACE ($B = 0.067$, $SE = 0.033$, 95% CI [0.010, 0.138]). Similarly, DunedinPACE mediated the relationship between stress and functional performance ($B = -0.010$, $SE = 0.005$, 95% CI [-0.020, -0.001]). Our findings suggest that perceived stress could play a crucial role in CLBP outcomes via an accelerated pace of biological aging. Further research should investigate the epigenomic impact of prolonged stress in individuals living with CLBP. Funding from NIH/NIAMS - R01AR079178 (PI: Aroke) and NIH/NIMHD - R01MD010441 (PI: Goodin).

High Impact Knee Pain Moderates the Relationship Between Interoceptive Sensitivity and Resting State Functional Connectivity Within the Salience Network

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Interoception, the ability to sense internal bodily states, is impaired by chronic pain due to dysregulation in the anterior insula (aINS) and anterior cingulate cortex (ACC), key nodes of the salience network (SN). However, underlying neurobiological mechanisms at the intersection of chronic pain and interoception remain unexplored, particularly in older adults despite greater pain prevalence and reduced interoception in this population. To address this gap, we investigated changes in resting-state functional connectivity (rsFC) within SN related to chronic pain impact in older adults with knee osteoarthritis (kOA) and examined interoception's modulatory role on this effect. Thirty-eight older adults with kOA (mean age=66.21 years) were stratified into low, medium, and high impact pain using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) reflecting the degree pain limits a person's daily life and activities. Interoception was assessed with Multidimensional Assessment of Interoceptive Awareness (MAIA). General Linear Models were used to predict rsFC within the SN at rest, controlling for age and sex. Participants with high impact pain exhibited less rsFC between ACC, aINS, rostral prefrontal cortex, and the supramarginal gyrus (FDR; $p<0.05$). A pain impact-MAIA interaction analysis revealed that higher interoceptive attentional regulation—the self-reported ability to focus and sustain attention on bodily sensations—was significantly associated with higher left aINS-ACC rsFC in the low impact pain group ($p<0.003$), whereas this relationship was non-significant in individuals with medium or high pain. These findings suggest that medium and high impact pain may disrupt key mechanisms in interoceptive processing in the older population.

Characterization of Systemic and Local Mediators Driving Osteoarthritis and Multi-Organ Aging

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Osteoarthritis (OA), or the loss of cartilage lining articular joints, is a leading cause of chronic pain. Existing pain management strategies are inadequate, and underlying OA pain mechanisms are unclear. Our lab and others are reframing OA as a systemic disease of the whole patient, and we aim to understand OA pain progression across the lifespan. We hypothesize that systemic, age-related factors secreted by fat in serum—particularly complement factors and lipids—drive OA pain. Young (16 weeks) and old (6 months) mice underwent lateral destabilization of the medial meniscus (DMM), sham, or no surgery (naïve), and were sacrificed at 28 weeks and 24 months. Pain sensitivity was assessed using pressure-pain hyperalgesia, joints were analyzed histologically, and serum underwent untargeted proteomic and metabolomic profiling. Aged DMM mice exhibited greater joint degeneration, osteophyte formation, and pressure-pain hyperalgesia compared to aged sham and young mice. Aged sham mice also demonstrated severe joint damage and pain compared to naïve aged mice. Proteomic and metabolomic analyses identified linoleic acid - a lipid associated with pain - elevated in young DMM mice, but not in aged counterparts, aligning with reduced sensitivity in aged mice. Distinct injury-associated systemic signatures included elevated cardiolipins, complement proteins, and metabolites associated with cardiovascular and metabolic comorbidities. These data suggest that DMM-induced OA not only reprograms the joint microenvironment and induces pain but could contribute to a decline in whole-body health. Our ongoing work aims to identify serum OA pain mediators as systemic therapeutic targets for chronic musculoskeletal pain management across the lifespan.

Ecological Pain and Physical Activity Volume and Patterns in Older Adults
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Chronic pain is associated with lower physical activity (PA) levels in older adults. However, pain characteristics change over time, and the impacts of changes in pain levels on daily PA quantities and patterns remain unknown. The PRIME pilot study recruited 30 older adults (mean age=74.1±6.0y) with multisite pain (32 pain sites in shoulder, elbow, hand/wrist, back, hip, knee, or ankle/foot) in Pittsburgh area in Pennsylvania. Pain characteristics (e.g., severity, laterality, interference) were measured using questionnaires during the clinic visit. After the clinic visit, ecological pain was assessed using Qualtrics surveys four times a day, along with Actigraph accelerometer assessment on the non-dominant wrist for 14 days. Linear regression models showed that participants with back pain had significantly lower activity counts (b=-493,271, p=0.020), higher activity fragmentation (b=5.0%, p=0.005), and fewer active minutes (b=-88.4, p=0.017). Number of pain sites and severity of hand/wrist pain decreased over a day (b=-0.08, p=0.019; b=-0.09, p=0.042, respectively) but tended to be stable across 14 days. Linear mixed models showed that every one-unit higher in overall pain severity at one time point was associated with 28,480 fewer activity counts at the subsequent time point (p=0.012), and these associations were weaker at later time points over a day (p=0.011). The severity and distribution of pain vary throughout the day, and the impact of pain severity on daily activity weakens as the day progresses. Individualized pain management programs should be provided to older adults with varying pain characteristics, particularly early in the day.

Senescence-Associated Secretory Phenotypes in Middle-to-Older Age Individuals with High Impact Pain at Risk for Knee Osteoarthritis

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Senescence-Associated Secretory Phenotype (SASP) contributes to tissue degeneration and inflammation, but its role in relation to pain-impact and osteoarthritic (OA) processes remains poorly understood. We hypothesized that SASP-related markers would be associated with aging, high impact pain, and/or OA severity. A subset of middle-to-older age individuals (>45-85) part of a larger, multi-site study self-reported pain impact, and underwent knee x-rays, and blood draws (n=72). Hierarchical cluster analysis identified empirical clusters based on combined pain-impact and radiographic OA. We evaluated senescence markers using MILLIPLEX® technology, with cluster and sex as between-subject factors considering age, ethnicity/race, study site, and BMI (alpha<0.05, Bonferroni post-hoc corrections). IGF-I was significantly greater in females compared to males with high impact pain but no radiographic OA (corrected-p=0.010), while females with high impact pain but no radiographic OA had significantly greater IGF-I compared to females with high impact pain and radiographic late-stage OA (corrected-p=0.003). IGF-II was significantly lower in males with high impact pain, but no radiographic OA compared to pain-free/no-OA males (corrected-p=0.009). Within the pain-free/no-OA cluster, females compared to males had lower IGF-II (corrected-p=0.039). Activin A, GDF-15, TNFR1/TNFRSF1A were associated with age and BMI; while IL-15, Osteopontin/OPN and Fas/TNFRSF6 were only associated with age. Several senescence markers (GDF-11, CCL3, CCL11, MOP-1alpha, Human Beta-2 Microglobulin) were not associated with hypothesized variables. Our results highlight the complexity of pain interactions with cellular senescence processes, and the important consideration of age, sex, and obesity when studying pain if we are going to develop early therapeutic targets for high impact OA-pain.

Hope As A Predictor Of Physical Activity Behavior In Older Adults With Musculoskeletal Pain

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Musculoskeletal pain is a barrier to physical activity (PA), enhancing functional decline in older adults. Thus, identifying psychological factors that promote PA in older adults with musculoskeletal pain is warranted. Prior research shows the psychological construct of hope predicts the frequency of exercise in healthy younger adults. However, the impact of hope on PA behavior in older adults with musculoskeletal pain is unknown. This observational study was designed to determine whether hope predicted self-reported and objective PA levels in older adults with musculoskeletal pain. Fifty-two older adults (age range 55-84 years) completed all assessments. Participants completed questionnaires to assess hope (Adult Hope Scale), self-reported PA (PA Scale for the Elderly), bodily pain (SF-36), kinesiophobia (Tampa Scale of Kinesiophobia), and pain catastrophizing (Pain Catastrophizing Scale). Participants also wore accelerometers on the hip for one week to objectively measure PA levels. Correlations were conducted to determine relationships between variables. Hierarchical regressions were conducted

to determine whether hope predicted self-reported and objective PA levels after controlling for relevant demographics, pain, and other psychological variables. After controlling for bodily pain, hope significantly predicted self-reported PA and was associated with greater PA levels. Bodily pain, but not hope, significantly predicted average daily steps derived from the accelerometer. Lower bodily pain was associated with more daily steps. Clarifying the role of hope in the PA behavior of older adults could present a novel target for intervention.

High-Impact Pain and Risk of Subjective Cognitive Decline Among Older Adults
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Chronic pain is associated with cognitive decline and increased risk of Alzheimer's disease (AD). Subjective cognitive decline (SCD), defined as self-reported worsening of cognitive function without objective impairment, is an early indicator of cognitive decline in the preclinical stage of AD. This study evaluated the relationship between high-impact pain (HIP) and SCD among older adults, using nationally representative data from the Health and Retirement Study (HRS) 2010-2020.Cross-sectional analyses of HRS 2010 data (N=16,173) examined SCD prevalence across pain-impact levels: no pain, low-impact pain (LIP), and HIP. Logistic regression models estimated odds ratios (ORs) for SCD. Cox proportional hazards models (2010-2020) assessed hazard ratios (HRs) for incident SCD among those without SCD at baseline (N=12,669). Models were adjusted for demographics, education, comorbidities, and survey design. In 2010, SCD prevalence increased with pain-impact severity: 17.3% for no pain, 24.8% for LIP, and 31.5% for HIP (P<0.0001). Analyses showed higher prevalence odds of SCD for HIP compared to no pain (aOR 1.78, 1.61-1.97) and LIP (aOR 1.24, 1.05-1.45), as well as LIP compared to no pain (aOR 1.44, 1.25-1.67). Longitudinally, HIP predicted greater SCD risk compared to no pain (aHR 1.43, 1.30-1.59) and LIP (aHR 1.25, 1.10-1.43), with LIP posing a greater risk than no pain (aHR 1.15, 1.01-1.31).High-impact pain is associated with higher prevalence of SCD and an increased risk of incident SCD among older adults. These findings underscore the need for comprehensive pain management strategies to potentially reduce cognitive decline in aging populations with chronic pain. NIA (T32AG049673, U01AG009740).

Navigating Pain Management in Older Adults with Advanced Chronic Kidney Disease: Qualitative Insights from Clinicians
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Chronic pain is common among older adults with advanced chronic kidney disease (CKD stage 4, stage 5, and end stage renal disease). However, the pharmacological management of their pain is difficult due to impaired renal clearance and the high risk of side effects. Despite published recommendations, little is known about how clinicians actually manage pain in this population. In a qualitative study using semi-structured interviews, twenty-four clinicians, physicians and advanced practice providers, from primary care, geriatrics, nephrology, and palliative care were recruited and interviewed. Interviews were transcribed and analyzed. Four major results were

identified. 1) In addition to assessing pain etiology, prior medications, and medication side effects, clinicians weigh patient values and perceived barriers (i.e., function, transportation, and finances) to determine a treatment plan. 2) Perceptions of risk and benefits for opioid therapy varied by clinician specialty. 3) Multiple clinicians are often involved in pain management, and clinicians desire processes that could improve this collaboration and patient care: “There’s kind of fractured care there which makes it hard.” 4) Across specialties, there was minimal formal education for managing pain in CKD: “I think it’s been trial by fire… so it’s been just kind of reading different things, anecdotal from… mentors and people who’ve had experience in pain and palliative care.” In summary, these findings highlight the complexities and challenges faced by clinicians across multiple specialties who manage pain for older adults with advanced CKD and emphasize the need for enhanced education and interdisciplinary collaboration to optimize patient care.Funding: K12NS130673.

Offset Analgesia Reduces Pain During Exercise: Older Adults Demonstrate Less Relief Than Young Adults

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The purpose of this study was to determine if offset analgesia (OffA) can be elicited with exercise. Forty-nine young (24 women; 21.8 ± 2.0 years, 25 men; 23.4 ± 5.7 years) and 36 older adults (17 women; 68.8 ± 7.4 years, 19 men; 72.6 ± 8.4 years) completed two sessions. In the first session, thermal OffA testing was performed, followed by exercise testing with exercise intensity instead of temperature as the offset stimulus. Control or offset exercise tasks were randomized and consisted of isometric knee extension at 25% of maximal voluntary contraction (MVC) force. Once moderate pain (5/10) was reported, either the control or offset portion of the exercise task began. For the control task, force was maintained for 25 seconds. For the offset task, force increased to 50% MVC for 10 seconds before returning to the initial force (25% MVC). Pain was reported 5 and 20 seconds after reaching moderate pain. Thermal and exercise OffA were similarly calculated as a percentage decrease in pain ratings comparing the offset and control tasks. Young and old adults demonstrated similar thermal OffA (young: 28.0 ± 40.0%, old: 20.1 ± 33.8%, $p=0.35$). Young adults demonstrated greater exercise OffA (34.8 ± 31.2%) than older adults (18.3 ± 29.4%) ($p=0.02$). Older adults exercised longer (211.5 ± 120.3s) than young adults (107.6 ± 63.3s) before reaching moderate pain ($p<0.001$), and those who reported moderate pain sooner demonstrated greater relief ($F(1,76) = 7.9$, $p=0.006$). OffA has potential as a clinical tool to improve exercise tolerance.

Pain Epidemiology

Assessing the Efficacy of Multimodal Approaches in Chronic Pain Management

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Chronic pain management guidelines recommend multimodal strategies, combining therapies, such as pharmacological, psychological, and complementary approaches, for improved clinical outcomes and fewer adverse events. This study evaluates the efficacy of multimodal pain

management strategies based on self-reports using data from the 2019 National Health Interview Survey (NHIS), a nationally representative sample of U.S. adults. Participants with chronic pain (n = 1,205) were grouped into three pain management categories: nonopioid-only, opioid-only, and opioid-involving multimodal, with the opioid-involving multimodal strategies further divided into opioid +: restorative/behavioral, complementary, or other therapies. Logistic regression analysis, using opioid-only as the reference group, found no statistically significant differences in the efficacy between the groups: OR=1.13 (95% CI: 0.88, 1.44; p=0.33) for opioid-involving multimodal vs. opioid-only and OR=1.01 (95% CI: 0.88, 1.44; p=0.97) for nonopioid-only vs. opioid-only. These results are further highlighted by the comparable efficacy of 71.25% of patients indicating their strategy to be effective in nonopioid-only group and 73.83% in opioid-involving multimodal to 71.38% in opioid-only treatments. Notably, younger individuals more frequently used nonopioid-only approaches, with higher education and income positively associated with nonopioid strategies. Although no significant differences were identified regarding the efficacy, these findings suggest that nonopioid therapies are effective for chronic pain management. Moreover, opioid-involving multimodal strategies may act as a bridge to help patients transition to nonopioid treatments from opioid medications without losing efficacy. Further investigation is needed to assess the long-term benefits and risks of these multimodal chronic pain management strategies.

Healthcare Access and Quality Among Adolescents with Co-Morbid Chronic Pain and Obesity: Insights from a National Survey

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Chronic pain and obesity (CPO) are two highly prevalent health issues among the adolescent population. These conditions can often cause or worsen one another, leading to compounding complications and increased risk of long-term chronic disease. Using the data from the 2021-2022 National Survey of Children's Health (NSCH), our study examines the care gaps, healthcare access barriers, and quality of care among adolescents with CPO (n = 730) compared to adolescents with chronic pain-only (n = 2805) and obesity-only (n = 4011). In terms of healthcare access, 15% of adolescents with CPO were unable to receive the healthcare they needed compared to 13% and 5% in the chronic pain-only and obesity-only groups, respectively, with mental health and dental care most frequently missed. The primary barriers to accessing care were appointment scheduling issues, cost, and the unavailability of services in their area. We further investigated healthcare quality through a parental response survey. Here, parents of adolescents with CPO reported a higher proportion of negative or absent interactions with doctors compared to those whose children had either chronic pain or obesity alone across all physician-patient interaction variables. Our study highlights the larger access barrier and lower quality of care received by the adolescent CPO population. Since CPO can severely diminish an adolescent’s quality of life, early and effective intervention of chronic pain or obesity is needed to prevent the progression to CPO.

Phenotyping Methods in EHR: Chronic Overlapping Pain Conditions and Mental Health Disorders within the Million Veteran Program.

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Electronic Health Records (EHR) are widely used in epidemiological and genetic research, often relying on phenotype algorithms to define lifetime cases and controls. We compared two phenotyping methods: "single-threshold" (ST) for cases with ≥1 diagnostic code and "multiple-threshold" (MT) for those with ≥1 inpatient or ≥2 outpatient diagnostic codes. We analyzed EHR data from 950,426 (90% men) Veterans in the Million Veteran Program, comparing ST- and MT-defined prevalence and relationships of chronic overlapping pain conditions (COPCs; migraine, tension headache, back pain [BP], fibromyalgia, irritable bowel syndrome, temporomandibular disorder [TMD], chronic fatigue syndrome [CFS]) and psychiatric disorders (major depressive disorder [MDD], post-traumatic stress disorder [PTSD], generalized anxiety disorder, social and simple phobias, panic disorder, agoraphobia, opioid use disorder) using tetrachoric correlations and exploratory and confirmatory factor analysis (EFA/CFA). ST prevalence was higher than MP prevalence, including BP (58.1%), CFS (14.7%), MDD (41.5%), and PTSD (32.6%). The MT method excluded an average of 33% of potential cases, from 11% for PTSD to 62% for TMD. Average tetrachoric correlation using ST was r=0.41 (0.18-0.69, SD=0.13) for COPCs and r=0.22 (-0.02-0.52, SD=0.12) for psychiatric disorders. We evaluated 2-6 factor models using EFA and CFA on split halves of the sample. A correlated four-factor model capturing mood, anxiety, pain, and headache disorder domains provided the best fit using both methods (ST: CFI=0.95, TLI=0.94, RMSEA=0.05, SRMR=0.03; MT: CFI=0.94, TLI=0.92, RMSEA=0.06, SRMR=0.04). Stricter definitions enhance specificity but may exclude cases, introducing bias and limiting generalizability. These trade-offs must align with study goals and disorder characteristics.

Use Of Non-Pharmacological Interventions By Adults With High-Impact Chronic Pain In The United States: A Cross-Sectional Analysis

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Few studies compare the differences in use of non-pharmacologic interventions (NPIs) between those with high-impact chronic pain (HICP) and low-impact chronic pain (LICP) or describe differences in use of NPIs by pain location. We addressed these gaps directly using data from the 2019 National Health Interview Survey. We described the use of NPIs stratified by pain impact and then used survey-weighted logistic regression models, adjusted for demographics, to examine the association between using ≥1 NPI and pain location. The estimated prevalence of US adults with chronic pain was 19.9% (95% CI: 19.5-20.0), with 36.4% (95% CI: 35.1-38.0) of tttthat group having HICP. Of those with HICP, 69.7% (95% CI: 67.6-71.9) reported using ≥1 NPIs in the past three months, compared to 62.9% (95% CI: 61.1-64.6) with LICP. The most frequently used NPI was physical, rehabilitative, or occupational therapy (25.9%, 95% CI: 24.0-27.9), and the least used was a peer support group (2.7%, 95% CI: 2.0-3.6). Among those with HICP, back pain (OR=1.52, 95% CI: 1.19-1.95) and upper extremity pain (OR=1.26, 95% CI: 1.003-1.59) are associated with greater use of any NPIs compared to those with HICP and no pain at these sites, respectively. Our findings highlight that most US adults with HICP have recently used NPIs to manage their pain, but use of different NPIs varied considerably and the

odds of using NPIs were different depending on pain location. Future work should examine barriers contributing to differential access to or use of NPIs by pain location.

A Survey of Social Determinants Impacting Musculoskeletal Pain in Chicago
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Joint pain is the leading cause of disability and influenced by socioeconomic status, and understanding these factors is essential for developing interventions to address musculoskeletal health disparities. This study aimed to screen socioeconomic factors affecting joint pain in areas of Chicago with health disparities. Surveys were collected in the six health equity zones of Chicago that include Northwest, West, North/Central, Southwest, Near South, and Far South. Surveys, distributed online and in-person, included questions on pain intensity and location, work, exercise, lifestyle, diet, mental health, healthcare, stress, and demographics. Eligibility criteria required participants to be Chicago residents and be 18 years or older. Over eight months, 234 surveys were collected, with most participants reporting back (31.7%) and/or knee pain (25.0%). The sample included 44% Caucasian, 27% African American, and 8.9% mixed race participants. Pain intensity was related to income, ethnicity, education, healthcare insurance in univariate analysis. Similarly, lifestyle factors (alcohol, smoking, diet) were related to ethnicity, income, education, and health insurance, while depression indices were linked to income and health insurance. Caucasian participants cited work (14%) and money (21%) as their top stressors, while African American participants identified family responsibilities (17%) and money (17%). Findings suggest pain, lifestyle factors, and depression are influenced by sociodemographic factors in Chicago. Limitations include a small sample size and overrepresentation of Caucasian participants with higher education. Future directions include expanding the sample size to be more inclusive of Chicago populations in all health equity zones as well as a multivariate analysis.

Older Adults with Lower Chronic Pain Self-Efficacy Have Worse Function and Quality of Life
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Chronic pain self-efficacy refers to a person's confidence in coping with chronic pain. Chronic pain is highly prevalent in older adults, with detrimental impact for these individuals. Prior research suggests that lower pain self-efficacy is associated with poorer functional status. However, this relationship has not yet been assessed in a large, nationally representative sample of older adults with chronic pain from multiple etiologies. This study aimed to assess the relationships between chronic pain self-efficacy and functional status and health-related quality of life (HRQOL) in a population-based sample of older adults. Participants were 1,296 older adults (age ≥65) with chronic pain (pain on more than half the days in the past 3 months) who were recruited from the AmeriSpeak® Panel, a probability-based panel representative of the U.S. population. Participants completed the Chronic Pain Self-Efficacy Scale and measures of pain severity (PEG scale); physical (PROMIS-10a) and cognitive (Attentional Function Index)

function; and HRQOL (PROMIS-Global-10). Linear regression analyses examined the associations between chronic pain self-efficacy and pain severity, functional status, and HRQOL. Pain self-efficacy was negatively associated with pain severity ($p < .01$). After adjusting for pain severity, lower pain self-efficacy scores were associated with poorer physical and cognitive function and HRQOL (all $p < .01$). This population-based study is the first to demonstrate that older adults who are less confident in their ability to cope with chronic pain have worse physical and cognitive function and HRQOL. Future research will evaluate interventions to improve pain self-efficacy for older adults from diverse backgrounds. Funding: NIH R01AG064947.

Early Life Adversity Increases Risk for Chronic Posttraumatic Pain, Data from Humans and Rodents

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Traumatic stress exposures (TSE) are common in life. While most individuals recover following a TSE, a substantial subset develop adverse posttraumatic neuropsychiatric sequelae such as chronic posttraumatic musculoskeletal pain (CPMP). Vulnerability factors for CPMP are poorly understood, which hinders identification of high-risk individuals for targeted interventions. One known vulnerability factor for many pain types is exposure to early life adversity (ELA), but few studies have assessed whether ELA increases risk for CPMP. This study used data from the AURORA study, a prospective human cohort study of TSE survivors, to test the hypothesis that ELA increases risk for CPMP. In addition, in secondary analyses, we assessed which subtypes of ELA (including childhood bullying) were most predictive of CPMP and whether a rat ELA model consisting of neonatal limited bedding (NLB), combined with single prolonged stress (SPS) in adulthood, would accurately model human findings. In AURORA study participants ($n=2,480$), using multinomial logistic regression modeling of four identified latent pain classes, we found that ELA increased vulnerability to the high unremitting pain class ($OR=1.047$, $p<0.001$), the moderate pain class ($OR=1.031$, $p<0.001$), and the moderate recovery pain class ($OR=1.018$, $p=0.004$), with physical abuse, emotional abuse, and bullying being the strongest predictors of high pain class assignment. Similarly, in male and female Sprague Dawley rats, in comparison to SPS alone NLB combined with SPS caused increased baseline sensitivity and prolonged mechanical hypersensitivity ($F(11,197)=3.22$, $p<0.001$). Further studies in animals and humans are needed to understand mechanisms by which ELA confers vulnerability to CPMP.

Demographic And Socioeconomic Characteristics Do Not Affect Fibromyalgia Impact Among Fibromyalgia Patients In The Us Midwest

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Fibromyalgia is characterized by chronic pain, fatigue, sleep problems, and cognitive impairment. The Fibromyalgia Impact Questionnaire-Revised (FIQR) is widely used to assess

fibromyalgia severity, which is influenced by many factors. We aimed to evaluate the affect of demographic and socioeconomic characteristics on FIQR in fibromyalgia patients in the US Midwest. This retrospective study consists of baseline data from 685 participants from the Fibromyalgia Activity Study with TENS (FAST) and Fibromyalgia Transcutaneous Electrical Nerve Stimulation in Physical Therapy Study (FM-TIPS). Survey data were collected using REDCap and included demographic and socioeconomic characteristics, movement-evoked pain and fatigue, Brief Pain Inventory (BPI), Multidimensional Fatigue Assessment (MAF), Pain Catastrophizing Scale (PCS), Widespread Pain Index (WPI), and FIQR. Stepwise regression analysis was used in statistical analysis. Study participants were 50.6±14.2 years, 96% were female, and 52% were unemployed. The participants reported movement-evoked pain 5.6±2.2, movement-evoked fatigue 5.8±2.4, BPI severity 5.8±1.6, BPI interference 6.1±2.0, PCS 22.6±13.5, WPI 11.0±4.3, and FIQR 56.8±16.9. After the stepwise model selection, demographic and socioeconomic characteristics did not stay in the final multivariable model for the outcome of FIQR. Instead, six pain and fatigue variables (BPI Interference = .43, MAF GFI =.22, BPI Severity =.19, PCS=.10, WPI= .07, movement-evoked fatigue=.06) explained 69.8% of the variation in FIQR [$F(6,617)=234.86$, $p<.001$]. In contrast to prior studies, demographic and socioeconomic characteristics did not significantly predict FIQR. Demographic and socioeconomic characteristics may have variable influence on disease impact across different regions of the US. The Scientific and Technological Research Council of Türkiye (1059B192302101), NIH (4UH3AR076387-02, UM1-AR-063381).

Exploring the Relationships Between Insomnia, Mental Health, And Substance Use Disorders Among Those With Chronic Pain

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While the impact of pain on sleep and behavioral health has been explored, the risk for developing comorbid conditions and the interplay between these diagnoses are not as well understood. Our objective was to investigate the complex interplay between 4 conditions: insomnia, anxiety, depression, and substance use disorder (SUD) for those with chronic pain (CP) utilizing TriNetX, a large-scale, real-world healthcare database. We extracted patient data between 2014 to 2024 from TriNetX based on queries of ICD codes for chronic pain resulting in a dataset from n=8,540,180 individuals [created 11/26/2024]. We calculated (1) the prevalence of insomnia, anxiety, depression, and SUD using 2-year intervals and (2) the competing risk of developing one or more of these conditions among those with CP. The prevalence increased from 2014 to 2024 for insomnia (5.9% to 18.3%), anxiety (15.0% to 41.5%), depression (13.3% to 31.3%) and SUD (11.3% to 22.2%) following a CP diagnosis. The absolute risk of developing these conditions within 3 years after a CP diagnosis was 4.7%, 16.3%, 7.8%, and 7.9%, respectively. All analyses showed an increased risk of developing at least one of these conditions within 3 years after CP diagnosis. For example, a person with CP and anxiety had a 29.2% risk of developing depression. In comparison, CP and SUD increased the risk of depression by 20.4% within three years of diagnosis compared to CP alone. These findings emphasize the need for holistic patient care, early detection, and comprehensive strategies for those with CP. Funding provided by: K12NS130673.

Correlating The Impact Of Biopsychosocial Factors On Experimental And Clinical Pain
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Pain involves a complicated interplay between biological, psychological, behavioral, and cognitive factors. Multiple studies have investigated correlations between experimental pain and clinically-relevant pain, attempting to determine the biopsychosocial factors underlying each. Currently, multiple knowledge gaps remain, partly due to insufficiently large patient samples that include both experimental and clinical pain measures, as well as a sufficient breadth of biopsychosocial measures that can serve as covariates. As such, we aim to investigate the contributions of biopsychosocial factors to variability in experimental pain versus acute postsurgical pain in a sufficiently large sample size. Approximately 1,000 patients undergoing abdominal, gynecological and urological surgeries were prospectively recruited over a 36 month period as part of the P5 perioperative study (NCT04864275). Fourteen predictive biopsychosocial factors were assessed at baseline via self-reported surveys and objective tests, including pain catastrophizing, cognitive flexibility, resilience, anxiety, and depression. Experimental pain measures included pressure pain threshold, cold pressor task, and conditioned pain modulation. Clinical pain was assessed on postoperative day 1 via self-reported pain severity using numerical rating scale, and opioid requirements obtained from the EMR. We are waiting for completion of recruitment (in 4 weeks), and will present the following analyses: 1) Univariate and multivariable logistic regression models will be constructed testing the associations between the biopsychosocial factors and experimental pain responses, 2) similar models will be constructed for variables associated with clinical postoperative pain intensity and analgesic use, 3) mediation analysis will be performed assessing the effect of predictive factors on the relationship between experimental and clinical pain.

Toxic Exposures and Chronic Overlapping Pain Conditions in a Veteran Cohort: Gender-Specific Insights from the Million Veteran Program
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Chronic overlapping pain conditions (COPCs) include migraine, tension headache, irritable bowel syndrome, chronic back pain, fibromyalgia, chronic fatigue syndrome, and chronic prostatitis. Environmental toxicants may increase COPC risk, but this is underexplored in Veterans. Analyzing data from the Million Veteran Program, with 542,461 Veterans (91% men), we evaluated the association between self-reported toxic exposures (e.g., Agent Orange, biological/chemical warfare agents [BCWA], anthrax vaccine, pyridostigmine bromide [PB], petroleum combustion products [PCP], pesticides, and open-air burn pits), self-reported pain ratings (0 to 10), and the lifetime prevalence of electronic health record COPCs. Models were adjusted for age, gender, service eras, and military branch. Prevalence of COPCs ranged from 53.7% for CBP to 1.75% for fibromyalgia, while toxicant exposure ranged from 68.3% for PCP to 5.49% for PB. Women were more likely to have a history of COPCs, and men reported more toxicant exposure than women (both $p<.001$). Toxicant exposure was associated with higher pain ratings [average difference (3.42 vs. 4.32; $p<.001$)]. The strongest association was with BCWA (OR=1.43; 95%CI=1.41-1.46) and PB (OR=1.21; 95%CI=1.16-1.25). Toxicant exposure was

associated with higher odds of COPCs, with BCWA (average AOR=1.67; 95%CI=1.59-1.75), PB (average AOR=1.60; 95% CI=1.50-1.72), and open-air burn pits (average AOR=1.39; 95% CI=1.33 - 1.46) showing the strongest relationship. The strongest link was between FM and PB (AOR=3.04; 95% CI=2.78 - 3.31) and BCWA (AOR=2.59; 95% CI=2.39-2.79). Results showed stronger relationships between toxicant exposure and COPCs in men (average AOR=1.40 for men vs. 1.31 for women). Further research should explore the mechanisms underlying these associations.

Country-level Gender Inequality, Intimate Partner Violence, and Sex Disparities in Adolescent Chronic Pain: A Global Perspective

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Research on sex disparities in pain among adolescents has predominantly focused on individual bio-psychological factors, overlooking the pivotal influence of societal contexts. Using data from 244,097 adolescents 11-15 years (50.7% female) across 44 middle- and high-income countries in the 2018 Health Behavior in School-Aged Children survey, we examined sex disparities in chronic pain prevalence and how they were shaped by macro societal factors. In particular, we focused on two factors highly related to societal gender experiences: Gender Inequality Index (GII, a composite measure of gender disparities in reproductive health, empowerment, and economic participation) and prevalence of lifetime intimate partner violence (IPV) in women. The percentage point difference in chronic pain prevalence between females and males ranged from 0 to 18% across countries (overall 13%, I^2=87.0%) and the female-male prevalence ratio ranged from 1.01 to 2.16 (overall 1.71, I^2=86.9%). Multilevel logistic regression accounting for individual-level covariates revealed no significant associations between GII, IPV prevalence, and chronic pain; however, sex-specific effects were observed. Higher GII was associated with higher odds of chronic headache (OR=1.13, 95% CI 1.02-1.26) and chronic multisite pain (OR=1.15, 95% CI 1.01-1.30) in males. Higher IPV prevalence in women was associated with higher odds of chronic pain (OR=1.11, 95% CI 1.01-1.23) in females. Sex disparities in adolescent chronic pain are widespread but vary considerably across countries. Societal gender inequality may have nuanced influence on adolescents' experiences. Future research should explore the mechanisms linking violence to adolescent chronic pain and prioritize violence prevention to address global sex disparities in pain.

Prevalence and Predictors of High Family Impact in Chronic Pain: Findings from the 2023 National Health Interview Survey

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The epidemiology of chronic pain is well-documented, but its impact on families is underexplored. Using 2023 National Health Interview Survey data (n=29,522), we estimated the prevalence of chronic pain with high family impact, stratified by demographic, socioeconomic, and health factors. High family impact was defined as responding "most days" or "every day" to

the question: “Over the past three months, how often did YOUR pain affect your family and significant others?” Among respondents with high-impact chronic pain (HICP)—pain limiting life or work activities most or every day—we used Chi-square tests to identify unadjusted associations with high family impact. A purposeful model-building approach was used to construct a logistic regression model incorporating significant predictors and confounders after adjustment. An estimated 21.2 million (8.5%) U.S. adults experience HICP, while 9.8 million (3.9%) report high family impact of chronic pain. Among individuals with HICP, 46.3% reported high family impact, versus 3.2% of those with non-high-impact chronic pain. Predictors of high family impact included anxiety, depression, disability, abdominal/pelvic/genital pain, migraines, previous stroke, race, employment, age, and U.S. region. Family structure did not significantly predict high family impact, except for a protective effect observed in previously married individuals compared to those currently married, when there were no children in the household. Given that nearly half of individuals with HICP report significant family impact, further research into modifiable resilience factors or opportunities for psychosocial interventions are warranted. These findings underscore the need for holistic approaches that address both individual and family dimensions of pain.

Prevalence Of Chronic Pain Across Industries And Occupations In The United States Adult Workforce

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Since the early 2010s, chronic pain has emerged as a leading cause of disability in the U.S. workforce, driving productivity losses and healthcare costs exceeding $550 billion. While there are many potential occupational risk factors for chronic pain including repetitive tasks, heavy lifting, and psychosocial strain, its prevalence across specific sectors and occupations remains largely unexamined. This study aims to bridge this gap by examining chronic pain across major U.S. industries and occupational sectors in the United States. Study data was obtained from the 2021 National Health Interview Survey, which provides health insight for the U.S. adult population. Analysis, performed in STATA, excludes participants with insufficient industry, occupation, or self-reported pain data, focusing on daily pain as the outcome. We examined the prevalence of pain across major occupations and industries. As of 2021, approximately 20% of U.S. adults suffered from chronic pain, with a significant portion of this demographic being in the workforce. Statistical analyses identified elevated pain prevalences among workers in the following occupations: healthcare support (14.5%), construction/extraction (13.7%), installation/maintenance/repair (13.4%), and transportation/material moving sectors (11%). Similarly, industries with significantly higher pain rates included: construction (13%) and public administration (12%). These findings highlight the elevated prevalence of daily chronic pain in occupations and industries involving sustained physical strain, emphasizing work-related factors as potential risk factors for pain. Further research is needed to develop chronic pain workplace interventions and multidisciplinary treatments to address the needs of this vulnerable population.

Discrimination and the Prevalence of Pediatric Pain in Asian Americans

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Chronic pain affects 15-25% of youth and often persists into adulthood yet remains understudied in the pediatric population, especially in ethnic/racial minorities. Asian Americans (ASAMs), the fastest growing minority group in the US, are projected to account for ~10% of the US population by 2060 yet are often not included in chronic pain research. This knowledge gap is concerning given that ASAMs often face racial/ethnic discrimination, a known risk factor for chronic pain. This research aims to estimate the prevalence of chronic pain in ASAM youth and determine associations between racial discrimination and chronic pain prevalence. Data was extracted from the National Survey of Children's Health from 2016-2022 (n=279,547). Caregivers of children ages 6-17 years old reported whether their child had ever been treated or judged unfairly because of their race or ethnicity. Chronic pain was defined as frequent or chronic difficulty with repeated or chronic physical pain during the past 12 months. Rates of chronic pain by racial/ethnic group were identified for children ages 0-17 years. ASAMs consistently reported lower rates of chronic pain each year (~2-4.5%) compared to their racial/ethnic counterparts (~4-10%) (Hispanic, Black, White, Other/multi-race)($p<0.0001$). However, we also found that ASAMs who reported racial discrimination had 3x greater odds of chronic pain relative to ASAMs who reported facing no discrimination (OR=2.8 95% CI: 1.5-5.2, $p<0.0001$). Further research should look at the role of discrimination in ASAM health experiences and consider ways to deliver care with cultural humility.

United States Adults with Chronic Pain Experience Profound Disparities in the Mental Health Patient Journey

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Clinical anecdote suggests that individuals with chronic pain (CP) may be less likely than others to use mental health (MH) treatment when needed. It is unclear whether differences in use of MH treatment are observable at the population level. We used data from National Health Interview Survey (n=31,997) to evaluate 3 inflection points in the MH patient journey: (1) the need for MH treatment, (2) the use of MH treatment, and (3) presence of unremitted anxiety or depression in the context of past 12-months (12m) MH treatment use. Logistic regressions controlled for insurance status, age, sex, race/ethnicity, cancer diagnosis, and functional limitations. Among those with MH treatment needs and co-morbid chronic pain, a minority (44.4%) had used MH treatment and screened negative for unremitted anxiety and/or depression. In comparison, 71.5% of U.S. adults who had MH treatment needs and did not have CP, had used MH treatment and screened negative for unremitted anxiety and/or depression. CP was associated with disparities across the MH patient journey: U.S. adults living with CP are (1) more likely to experience the need for MH treatment, (2) less likely to use needed MH treatment, and (3) more likely to screen positive for unremitted anxiety or depression symptoms when past 12m MH treatment was used. Suboptimal MH system performance is the most prevalent patient experience for U.S. adults with CP. Future research is needed to understand and address the mechanisms that underly the end-to-end MH disparities faced by those living with CP.

Exploring Gender Differences in the Link Between Chronic Overlapping Pain Conditions and Post-Acute COVID-19 Sequelae

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Chronic overlapping pain conditions (COPCs) are medically complex, intersecting conditions. The emergence of post-acute sequelae of COVID-19 (PASC), for which pain is a common symptom, has further complicated the chronic pain landscape. While women are more likely to have both COPCs and PASC, the role of gender identity in the association between COPCs and PASC remains unclear. This study assessed the impact of gender identity on a) prior COPCs and the odds of PASC and b) prior PASC and the odds of a COPC. Adults in the United States (N=2808) participated in an online survey. The average age was 41.5 years (SD=18.5), and most identified as women (52.9%), white (88.6%), and non-Hispanic/Latine (87.4%). Participants were asked to report the presence of seven COPCs both prior to and after COVID-19 infection. PASC status was also reported. Multivariate logistic regression models were utilized. Gender identity was included in interaction terms, and analyses were stratified to explore the role of gender identity in these relationships. Having a prior COPC was associated with significantly greater odds of PASC development, with a stronger association in men (aOR=3.87; 95% CI=2.75-5.43) than women (aOR=1.82; 95% CI=1.34-2.46). Having PASC was associated with similarly greater odds of subsequent COPC development among both men (aOR=7.42; 95% CI=5.01-11.00) and women (aOR=7.39; 95% CI=5.00-10.92). Considering prior COPCs may be helpful in assessing an individual's risk for PASC following COVID-19, particularly among men.

Disparities in the Management of High Impact Pain by Race and Hispanic/Latino Heritage

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Multidisciplinary pain management teams are considered the gold standard in pain management. Yet studies examining concomitant use of multiple healthcare provider types by pain patients are sparse. Given known disparities in pain management, we sought to investigate disparities in use of multidisciplinary pain management teams for high impact pain (HIP) by race and ethnicity.We examined N=6,908 HIP respondents from the 2016-2019 nationally representative Medical Expenditure Panel Survey (representing weighted N=64,360,249 individuals). We examined three outcomes: use of two or more healthcare provider types, use of only a primary care physician, and zero healthcare visits for HIP. Two or more provider types for pain management is consistent with recommendations; using only a primary care physician and zero healthcare visits are examples of inadequate pain management.Dominicans (21.40%; 95% CI, 10.57-38.56) and non-Hispanic (NH) Blacks (34.08%; 95% CI, 29.44-39.06) reported significantly lower use of two or more provider types for HIP than NH Whites (reference). For use of only a primary care physician, Mexicans (18.08; 95% CI, 13.79-23.34), NH Blacks (19.18%; 95% CI, 14.11-25.54), Central/South Americans (21.33%; 95% CI, 16.36-27.33), and Cubans (22.09%, 95% CI, 13.24-34.49) reported significantly higher prevalence than NH Whites. Cubans (44.51%; 95% CI, 28.85-61.35) reported the highest prevalence of zero healthcare visits for HIP.Use of multidisciplinary pain management varies in U.S. adults by race and Hispanic/Latino heritage. Future research should examine whether these disparities are also reflected in the use of

multimodal multidisciplinary approaches for pain management, such as concomitant use of pharmacologic and non-pharmacologic treatments.

Real-World Assessment of Patterns of Pain Treatment in Systemic Lupus Erythematosus: A Pathway Visualization Study Using Electronic Health Records
Nathan Le, Andrew Walker, Tricia Park, Selen Bozkurt, Titilola Falasinnu; Stanford School of Medicine

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease affecting 200,000 individuals in the U.S., predominantly women and racial/ethnic minorities, who face disparities in care. Chronic pain, including overlapping conditions like fibromyalgia and musculoskeletal pain, affects over 50% of SLE patients, contributing significantly to disease burden. Pain management strategies remain inadequately characterized, with reliance on steroids and opioids despite their risks and a lack of updated guidelines. This study analyzes electronic health records (EHR) to examine trends in pain management strategies for SLE from 2005-2024, highlighting demographic influences on treatment patterns. Data from 768 adult SLE patients at a Northern California academic center were analyzed. Sequence analysis was used to track transitions between corticosteroids, opioids, NSAIDs, and alternative therapies. Sankey diagrams and sunburst plots visualized treatment pathways over one year after initiation. Steroid use decreased from 59% (2005-2014) to 51% (2015-2024), while NSAID use rose from 19% to 29%. Opioid reliance declined from 28% to 23%. Younger patients and males in recent years used more multimodal therapies. Racial disparities in pain prescriptions narrowed, though Hispanic patients were more likely to receive multiple modalities. Pain management for SLE has shifted toward multimodal strategies, reducing reliance on steroids and opioids. These findings underscore the need for updated guidelines that account for demographic differences to promote equitable, evidence-based care and improve outcomes for patients with SLE.

Comparing Influential Variables for Low and High Recovery Expectations among Those with Lumbar Spinal Stenosis: A Network Analysis
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Lumbar spinal stenosis (LSS) is a degenerative condition that contributes to pain and disability. Recovery expectations (RE) are strongly associated with LSS outcomes and highlighting the most influential factors is important in health management. The purpose of this study is to 1) compare multivariate relationships of low (LRE) versus high recovery expectation (HRE) groups for participants with LSS and 2) identify which influential variables are different between these groups. We used baseline data from a prospective cohort study of patients with new visits for LSS and stratified participants into low (n=225) and high RE (n=108). A medium recovery group (n=259) was removed to compare RE extremes only. RE was assessed using a single-item measure (Likert:0-10) rating their confidence the symptoms will be gone/much better in 3 months. The variables of interest were chronicity and the PROMIS-29+2 measures for Anxiety, Cognition, Depression, Fatigue, Pain Interference, Participation, Physical Function, and Sleep Disturbance to explore relationships among the variables within each group. We performed

network analysis and calculated partial correlations and strength centralities to assess variable influence, tested stabilities of the networks, and compared networks using Global Strength Test (GST) with cumulative correlation weights. The network structures for each group were not different (GST: S=0.47, p=0.06) and reached acceptable to preferred levels of stability (CS-coefficient:0.361, 0.671). Anxiety and Participation strength centralities were more influential on other variables in the LRE than the HRE group ($p<0.05$). It may be important to further investigate Anxiety and Participation influences in those with low RE over time.

Specialty Healthcare Use Among Rural and Urban Veterans with Fibromyalgia
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Rural Veterans with chronic pain can experience barriers to accessing specialty pain care. The risk for suboptimal pain care may be magnified for Veterans with complex presentations. Veterans with Fibromyalgia typically present with multiple pain sites and commonly experience related symptoms such as fatigue, concentration difficulties, low mood, and disrupted sleep. To investigate the impact of rurality on pain care among patients with Fibromyalgia, a cohort of all Veterans seen for Fibromyalgia in the Veterans Health Administration in 2022 was created using national administrative data. Counts of primary and specialty care visits in the following year were calculated. Negative binomial regression was used to estimate differences in specialty care for rural and urban Veterans, adjusted for demographics and psychiatric and medical comorbidity. The cohort included 30,462 Veterans with Fibromyalgia, which included one-third rural Veterans (n=10,062). While overall visits for fibromyalgia were not different, rural Veterans had more primary care visits (Mean=1.5 rural versus 1.3 urban, $p<.01$) but fewer specialty care visits (Mean=1.1 and 1.4, $p <.01$): aIRR=0.88, 95% CI: 0.83-0.92. Also, Veterans who utilized a rural VA clinic for their primary care received significantly fewer specialty care visits, relative to those who received primary care from a medical center, independent of rural or urban residence status: aIRR=0.72, 95% CI: 0.66-0.78. Rural Veterans with Fibromyalgia used significantly less specialty care independent of care site, with Veterans receiving care at rural clinics having the lowest use rate. These Veterans may benefit from increased access to specialty pain care.
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Pain Neuroimaging

Exploring The Link Between Inter-Brain Dynamics, Patient-Clinician Relationship, And Treatment Outcomes In Chronic Pain.
Alessandra Anzolin, Arvina Grahl, Seneca Ellis, Lara Gardiner, Dieu Ni Doan, Jeungchan Lee, Ted Kaptchuk, Vitaly Napadow; Harvard Medical School

In chronic pain management, the quality of the patient-clinician relationship significantly influences treatment outcomes and patient satisfaction. This study investigated the impact of augmented (empathetic) versus limited (business-like) clinical contexts on inter-brain dynamics and patient-clinician relationships during acupuncture treatment. We analyzed EEG hyperscanning data from 33 dyads of chronic low back pain patients and acupuncturists during treatment and no-treatment conditions, alongside behavioral measures. Patients and clinicians

completed questionnaires post-interaction, including the Consultation and Relational Empathy (CARE) scale and the Warmth and Competence Scale (WCS). CARE and warmth scores were significantly higher in the augmented group compared to the limited group, validating the successful manipulation of the clinical context. Despite similar pain relief between groups, the augmented group reported greater improvements in mood, increased willingness to continue treatment, and higher expectations for future acupuncture benefits. EEG analyses revealed that the augmented group exhibited a higher number of patient-to-clinician inter-brain connections, particularly in brain regions associated with social mirroring (vlPFC, TPJ, STG, insula) and nociceptive processing (S1, M1, ACC). In particular, higher inter-brain connectivity was found during treatment conditions, suggesting enhanced social mirroring when patients recognized active pain management by the clinician. Additionally, a correlation study showed that greater information flow directed from patients to clinicians (density of brain-to-brain significant connections) is linked to increased acupuncture analgesia. These results underscore the critical role of clinical context in shaping both behavioral and neural correlates, offering novel insights into mechanisms linking therapeutic alliance and chronic pain management. R33-AT009306, Korea Institute of Oriental Medicine (KIOM)

Peak Alpha Frequency and Alpha Asymmetry as Potential Biomarkers of Pain Intensity and Treatment Outcomes in Chronic Pain Patients

Seneca Ellis, Alessandra Anzolin, Dieu Ni Doan, Arvina Grahl, Lara Gardiner, Jeungchan Lee, Ted Kaptchuk, Vitaly Napadow; Harvard Medical School

Despite the high prevalence and debilitating nature of chronic pain, individual variability in response to pain treatment is not well understood. In recent years, there has been a push to identify biomarkers that may explain variability in the pain experience, as well as guide new and/or personalized treatments. Electroencephalography (EEG)-based measures, specifically in the frequency band Alpha, have been proposed as possible candidates, given the marked difference in chronic pain patients compared to healthy controls. The current study investigated several Alpha band features in relation to baseline pain levels, response to pain treatment, and pain catastrophizing. Patients with chronic low back pain underwent resting state scans and a cuff-pain task followed by an acupuncture treatment for their pain. Using the resting state data, we extracted two variables of interest: frontal alpha asymmetry (FAA) and peak alpha frequency (PAF). Our analysis revealed a significant correlation between FAA and average pain levels over the past four weeks, aligning with prior research on evoked pain. Furthermore, FAA demonstrated a positive association with pain catastrophizing scale (PCS) scores, specifically in rumination and helplessness. Additionally, we found that faster sensorimotor PAF was associated with a greater reduction in pain following the acupuncture treatment. These results suggest that FAA and PAF code for different brain mechanisms and are linked in different ways to the experience of chronic pain. FAA may be a useful biomarker in understanding pain intensity and cognitive-affective responses to pain, while PAF may be useful in predicting treatment outcomes in chronic pain patients.

Functional Connectome Fingerprinting of People with TMD and their subjective pain experience

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Functional connectome fingerprinting has allowed for the individual identification of participants as well as the exploration of what connections are driving these individual differences. (Finn et al. 2015, Amico et al. 2018). Recent advances in the use of fingerprinting have shown that the method can be used to predict pain thresholds (Tu et al. 2019) as well as correlate with individual experiences (Tolle et al. 2024). Using these findings, in this study we examined resting-state functional fingerprints and differences in predictability of pain between healthy controls and participants with temporomandibular disorder (TMD). No identifiability differences were found between groups. Exploring idiosyncrasy, we found that healthy controls had higher idiosyncrasy in connections with visual or somatomotor networks, while participants with TMD had higher ICC values in connections with the default-mode network (DMN). Participants with TMD showed higher ICC strength in DMN, while controls showed increased ICC strength with somatomotor and salience networks. Using the connections that were more idiosyncratic for controls, we found that identifiability became lower in TMD participants. Principal component analysis of idiosyncratic connections in TMD showed moderately correlated with average pain ratings from quantitative sensory testing results. These findings show that subjects of both groups can be identified using whole brain parcellations, but that they can be separated by taking a subset of the connectome that is idiosyncratic to each group thus optimizing differentiation. Similarly, creating components from idiosyncratic connections for participants with TMD allows for the prediction of how participants will perceive QST pain.

Pain and the Brain: Using fMRI to Identify the Brain Representation of Pain Evoked by Punctate Mechanical Stimuli and Mechanical Hyperalgesia in Healthy Subjects

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Neuropathic pain is often accompanied by mechanical hyperalgesia (MH). Primary MH is exacerbation of pain at the injury site, whereas secondary is enhanced pain beyond that site. Secondary MH is associated with enhanced central nervous system nociception. The capsaicin-heat pain (C-HP) model can induce secondary MH. fMRI evaluated 1) brain substrates underlying pain to weighted punctate mechanical stimuli (WPMS) to the leg, and 2) changes following central sensitization. 47 volunteers (25F, 27±5 y/o) underwent fMRI for a series of 27 WPMS of 3 forces: 128, 256, 512 mN. Separately, 31 volunteers (18F, 28±6 y/o) underwent the same fMRI protocol before and after C-HP induction. Subjects rated pain intensity via numerical rating scale (0-100) for each force after each fMRI session. We found significant activation in our global exploratory analysis with all 3 stimuli in the L cingulate gyrus (anterior division) and R postcentral gyrus. In our hyperalgesia cohort, a two-way repeated measures ANOVA for reported pain ratings detected: 1) a significant main effect of condition, indicating that C-HP successfully induced secondary MH, and 2) a significant main effect of stimulus intensity, showing that we elicited different levels of pain. fMRI group analysis revealed a significant contrast for after>before C-HP in the R middle frontal gyrus and R superior frontal gyrus. We determined two major findings: 1) representation for mechanical pain colocalized with regions associated with acute thermal pain processing, and 2) development of hyperalgesia was associated with increased activation in the R middle frontal gyrus and R superior frontal gyrus.

Preliminary Evidence of Reduced Neuroinflammation Following Median Nerve Release Surgery in Two Patients with Carpal Tunnel Syndrome

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Using [11C]PBR28 Positron Emission Tomography (PET) imaging, studies from our group have shown elevated levels of the 18kDa Translocator Protein (TSPO), a marker of neuroinflammation, in the brain of patients with various pain conditions (e.g., Loggia et al., 2015). However, whether this signal changes after treatment is unknown. To test this, we evaluated two patients with Carpal Tunnel Syndrome (CTS) undergoing median nerve release surgery (females, 52 and 77 years old). Both patients were scanned using a 3T Siemens Biograph mMR PET/MRI scanner before and three/four months after surgery. Pre- and post-surgical [11C]PBR28 PET maps, quantified as Standardized Uptake Value Ratio (SUVR) with the whole brain as a pseudo reference region, were spatially normalized to the MNI152NLin6Asym standard space (using FSL FNIRT) and smoothed (8mm FWHM). They were then compared by subtraction within the right Brodmann areas 1, 2, 3a, and 3b of the Jülich histological atlas (containing the primary somatosensory cortex, S1, contralateral to the symptomatic hand). Compared with the pre-surgical scans, the post-surgical scans exhibited marked signal reduction in/around the "hand knob" of S1, with regions partially overlapping in both patients (peak coordinates: [22, -28, 56] and [28, -30, 56], respectively). SUVR values for the first patient decreased from 1.094 to 0.894 and, for the second, from 1.118 to 1.010. These findings provide preliminary evidence of reduced neuroinflammation in the cortical hand area contralateral to the affected hand in CTS after surgical treatment. This work underscores the promise of TSPO PET signal as a potential treatment response marker.

Imaging the Role of Skull Bone Marrow Immunity in Chronic Low Back Pain: A Positron Emission Tomography Study

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Using [11C]PBR28 positron emission tomography (PET), our group demonstrated elevated levels of the translocator protein (TSPO), a putative marker of immune cell density, in the bone marrow of patients with Migraine with Aura (Hadjikhani, 2020). Similar TSPO PET signal elevations were subsequently reported in neurodegenerative disorders (Kolabas, 2023), supporting a role for skull immune activation in various disorders linked to neuroinflammation. The aims of this study were to 1) extend these observations to another chronic pain condition, chronic low back pain (cLBP), and 2) evaluate their relationship with aging and clinical symptoms. Eighty-four patients (mean age [SD]: 47 [19]) with cLBP underwent a 90-minute integrated [11C]PBR28 PET-MR imaging. Standardized uptake value (SUV) images were computed from 60-90 min PET data and normalized to the standard structural MNI152 template.

FSL-FEAT software was used to perform skull bone-focused voxel-wise multiple regression analyses to test the association between TSPO, age, and all PROMIS-29 questionnaire domains (physical function, anxiety, depression, sleep disturbance, ability to participate in social roles, pain interference, and pain intensity), correcting for genotype and, in PROMIS-29 domain analyses, age. The TSPO signal was negatively correlated with age in a widespread portion of the skull and, more focally, positively correlated with the severity of anxiety, depression, sleep disturbance, and pain interference (p's<0.001). These results suggest that skull bone marrow immunity may be linked to cLBP and its associated psychological and functional impairments, highlighting its potential role in pathophysiology of cLBP, and perhaps other conditions characterized by brain inflammation.

Brain Oscillatory Changes Across Menarche and its Relationship to Widespread Pain
Natalie Osborne, Frank Tu, Sarah Darnell, Lynn Walker, Kevin Hellman; Endeavor Health

Sex disparities in chronic pain become more pronounced after menarche (the first menstrual period), coinciding with a period of significant developmental changes in brain structure and oscillations. The role of brain oscillations in shaping pain phenotypes remains a topic of debate, partly due to a lack of large-scale longitudinal studies focusing on at-risk youth. To address this gap, this study followed 207 adolescents over an average of 2.6 years, capturing pre- and post-menarchal measures of pain and resting-state electroencephalography (EEG) activity. Pain was assessed through questionnaires (one week recall window) that included measures of pain intensity and interference, menstrual pain, and a body map identifying widespread pain, defined as pain in at least 3 out of 7 body regions. Resting-state brain activity was recorded using 64-channel EEG, with analyses focusing on oscillatory activity in the alpha, beta, theta, and gamma frequency bands. Twenty-five percent of premenarchal youth met criteria for widespread pain, while 29% met criteria for new widespread pain postmenarche. Between-subject analyses of premenarchal EEG data revealed that adolescents with widespread pain exhibited reduced theta activity compared to those without widespread pain, a difference that was not observed postmenarche. Within-subject analyses of EEG data showed a general decrease in theta activity following menarche in adolescents regardless of pain status. Thus, brain oscillatory activity undergoes significant changes across the menarchal transition, and the relationship between widespread pain and theta activity is influenced by menarche. These findings suggest that neurodevelopmental changes affect pain sensitivity during the menarchal transition. Funding: R01HD096332.

Impact of Psychological Factors on Fractional Anisotropy Measurements Derived from Diffusion MRI in Chronic Low Back Pain
John R Gilliam, Jennifer MC Vendemia, Sheri P Silfies, Stephen A Coombes; University of Florida

Studies report inconsistent findings on fractional anisotropy (FA) in chronic low back pain (cLBP), with some noting decreases and others no differences compared to healthy controls (HC). Previous FA comparisons between cLBP and HC did not adjust for prevalent psychological factors like anxiety and depressive symptoms. Emerging literature shows FA

decreases linked to anxiety and depressive symptoms, even in healthy individuals with subclinical symptoms. In this study, cLBP (n=44) and HC (n=41) differed significantly on the Center for Epidemiologic Studies Depression Scale (CES-D) and both components of the State-Trait Anxiety Inventory (STAI) ($p < .05$). Bartlett's Test confirmed correlation between measures of anxiety and depressive symptoms, justifying dimensionality reduction via principal component analysis. Tract-based spatial statistics on FA images generated a common white-matter skeleton. Voxel-wise comparisons between cLBP and HC were made, controlling for age, sex, and a principal component explaining over 80% of the variance in anxiety and depressive symptoms. No clusters showed greater FA in HC, but cLBP exhibited greater FA in several clusters. Significant clusters ($p < .05$) were found in the right corticospinal tract, bilateral external capsule, and left frontal aslant tract. FA differences in these regions may reflect adaptive neuroplastic changes due to altered motor demands, upregulation of nociceptive and emotional pain processing pathways, and increased cognitive resources for pain management and movement-related decision-making. These findings highlight the complexity of the biopsychosocial model. This is the first study to control for anxiety and depressive symptoms when comparing FA between cLBP and HC and to report greater FA in cLBP.

Application of Artificial Neural Networks and Functional Brain Connectivity to Inform Pediatric Headache

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Pediatric headache is a poorly defined disorder with unclear delineation between diagnostic sub-groups. The use of deep learning techniques, a branch of artificial intelligence (AI), has the capacity to shed light on relationships that have previously eluded investigation. We aimed to investigate the utility of artificial neural networks delineate pediatric subjects with headache from those who are otherwise healthy. We explored a series of techniques to determine the utility of AI methods in 1) compressing neuroimaging data, and 2) accurately classifying pediatric headache subjects based on neuroimaging. In a cohort of 1055 subjects from the Human Connectome Project, we trained and evaluated a variational autoencoder (VAE), autoencoder (AE), principal component analysis (PCA), fast independent component analysis (fICA), and uniform manifold approximation and projection (UMAP) on functional magnetic resonance imaging (fMRI) data that was processed into connectivity matrices. Source reconstruction was highest for the VAE model (R=0.828) and lowest for UMAP (R=0.52) in Pearson’s correlation. On an external cohort, the VAE model achieved modest reconstruction performance of around 70% accuracy for the 21 control (0.65) and 58 headache (0.63) cohorts. Feature importance analysis demonstrated the posterior division of the cingulate gyrus and its connection to the cuneal cortex to have the most remarkable impact on model accuracy. Preliminary findings support the pursuit of VAE models to understand functional neuroimaging data and should be explored to inform headache sub-groups with larger cohort sizes. NIH (R01NS125265) and Boston Children’s Hospital.

Increased Amygdala Response During Viewing of Stressful Images is Associated with

Decreased Parasympathetic Tone Among Individuals with Episodic Migraine
Michael Datko, Jack Schnieders, Alessandra Anzolin, Ludovica Brusaferri, Megan Heffernan, Hope Housman, Kassandra Round, Lillian Kinder, Alison Goldstein, Mackenzie Hyman, Melaina Gilbert, Frances Marin, Sarasa Tohyama, Eva Ratai, Robert Edwards, Bruce Rosen, Hsinlin Cheng, Zev Schuman-Olivier, Vitaly Napadow, Nouchine Hadjikhani, Marco Loggia, Riccardo Barbieri, Randy Hirschtick, Ronald Garcia; Harvard Medical School

Migraine is a highly prevalent and debilitating headache disorder characterized by dysregulation of the autonomic nervous system (ANS) and hypersensitivity to stress. While sensitivity of the peripheral and central ANS in migraine has been demonstrated independently, simultaneous effects of stressors on both components remain unexplored. We designed a stress challenge task using images with negative and neutral valence from the International Affective Picture System (IAPS) and measured central (via fMRI amygdala activation) and peripheral (instantaneous high-frequency heart rate variability, HF-HRV, from piezoelectric pulse monitors based on Barbieri et al., 2005) ANS reactivity in individuals with episodic migraine (MIG, n=83) and healthy volunteers (HV, n=21). Participants alternated between viewing blocks of negative- and neutral-valence images (6 images/block, 4s/image, 12 blocks/type, 144 images total, 15 min) with rest periods between blocks. For both measures, we examined the contrast between negative minus neutral blocks (NEG-NEU) and compared MIG versus HV. MIG showed greater activation during NEG-NEU in the right amygdala ($z>3.1$, $p<0.05$ FWE-corrected) and greater decreases in HF-HRV during NEG-NEU ($p=0.04$) compared to HV. Additionally, decreased HF-HRV in MIG was associated with increased left amygdala activity during NEG-NEU ($z>3.1$, $p<0.05$). These findings suggest that episodic migraine is associated with heightened central and peripheral ANS responses to stress, marked by amygdala hyperactivation and decreased parasympathetic tone. The association between decreased HF-HRV and increased amygdala reactivity underscores alterations in central autonomic regulation in response to stress in MIG patients, highlighting potential targets for interventions aimed at mitigating migraine-related stress reactivity.

Individualized Neural Networks Differ Based on Depressive Symptoms in Women with Urologic Chronic Pelvic Pain Syndrome
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Chronic pain and depression are often comorbid, however, the neurobiological mechanisms underlying their relationship remain unknown. In this study, we examined person-specific functional connectivity in 143 women with urologic chronic pelvic pain syndrome (UCPPS) with high and low depressive symptoms (indexed by composite scores from the Hospital Anxiety and Depression Scale) from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. Neuroimaging included a modified “resting state” fMRI specifically aimed to evoke brain activity related to symptoms of UCPPS by instructing participants to drink water before image acquisition. Taking an idiographic analytic approach, we applied group iterative multiple model estimation (GIMME) to estimate group-, subgroup-, and individual-level connections among 12 regions of interest previously identified as key hubs for chronic pain and depression. We assessed differences in node centrality (number of contemporaneous connections involving that node, relative to the total connections for that person) between depressed and non-

depressed UCPPS patients. For depressed patients, we found lower centrality in the left hippocampus and left temporal lobe, but higher centrality in the right inferior parietal lobe (all pFDR<0.01). Node centrality of the left temporal lobe and left thalamus predicted provoked pain sensitivity at the suprapubic region (measured by pain ratings when a 2 kg/cm2 pressure was applied to the area), while the latter also predicted widespread pain (indexed by a modified CHOIR body map with 76 regions). Together, these results suggest distinct neurobiological subtypes of UCPPS based on depressive symptoms.Funding: R01DK123164.

Neuroinflammation and Self-Reported Pain Widespreadness in People with Human Immunodeficiency Virus-Related Neuropathic Pain

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Our group has previously observed elevated levels of the 18kDa translocator protein (TSPO), a marker of neuroinflammation, in both people with chronic pain and people with HIV (PWH) using [11C]PBR28 positron emission tomography (Loggia et al., 2015; Sari et al., 2022). In this study, we hypothesized that a link may exist between neuroinflammation and self-reported pain widespreadness in PWH who also had neuropathic pain. Nine PWH (mean age [SD]: 57.89 [6.3]; 3 females, 6 males) were scanned with a 3T Siemens Biograph mMR PET/MR scanner. Using a T1-weighted volume for attenuation correction, standardized uptake value ratios were generated from 60-90 min post-injection data, spatially smoothed (FWHM=8mm), and normalized to the MNI152 template using FSL and FreeSurfer. A whole-brain voxel-wise correlation was performed using FSL-Randomise with a cluster-forming threshold of z=2.3 and a cluster size threshold of p<0.05. Participants drew on a digital body map to indicate their pain sites, and the drawings were converted into a NIfTI format to compute the total pixel counts. After excluding two outliers based on the 1.5*interquartile range method, the final sample comprised 7 PWH (mean age [SD]: 57.86 [7.11]; 2 females, 5 males). Total pixel count (i.e., pain widespreadness) was significantly correlated with elevated TSPO levels (i.e., neuroinflammation) in regions involved in pain perception and processing, such as the pre-and postcentral gyri and the anterior cingulate, orbitofrontal, dorsomedial, dorsolateral, and ventromedial prefrontal cortices. The relationship between pain widespreadness and neuroinflammation provides insight into the mechanism behind the maintenance of neuropathic pain in PWH.

Brain Structure and Function and Pain Sensitivity in Autistic Adults

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Pain perception is a complex process involving emotional and sensory dimensions. Slower peak alpha frequency (PAF), a neural marker of cortical activity, has been associated with increased pain sensitivity in neurotypical individuals. The amygdala, a key limbic structure involved in emotional and sensory regulation, also plays a critical role in pain perception. In autism spectrum disorder (ASD), pain responses often diverge from typical patterns, manifesting as

hypersensitivity, hyposensitivity, or atypical pain processing. Despite these insights, the interplay between brain structure and brain function and pain perception remains poorly understood in ASD. To address this limitation, we examined pain intensity ratings, amygdala volume, and resting-state PAF in middle-aged individuals with ASD (N = 24) and age-matched neurotypical controls (N = 19). Pain ratings were assessed using a psychophysical heat stimulation paradigm. Amygdala volume was assessed using a T1-weighted MRI scan and Freesurfer. PAF was assessed using 128-channel EEG. T-tests revealed that pain ratings were significantly higher in the ASD group compared to neurotypical controls. No significant group differences were observed for amygdala volume nor PAF. Correlation analyses within the ASD group revealed that lower PAF was associated with higher pain ratings. Additionally, significant positive correlations were found between amygdala volume and PAF, while no significant relationships were observed between amygdala volume and pain ratings. These findings highlight divergent relationships between brain structure, brain function and pain perception in ASD, underscoring atypical sensory and emotional processing in this population.

Elevated Fractional Amplitude of Low Frequency Fluctuation Associations with Episodic Migraine Symptomatology

Jack Schnieders, Michael Datko, Ludovica Brusaferri, Sarasa Tohyama, Kassandra Round, Lilian Kinder, Megan Heffernan, Ronald Garcia, Randy Hirschtick, Eva Ratai, Robert Edwards, Bruce Rosen, Hsinlin Cheng, Zev Schuman-Olivier, Vitaly Napadow, Nouchine Hadjikhani, Marco Loggia; Harvard Medical School

Episodic migraine is a widespread, disabling pain condition with pathophysiology that includes cortical hyperexcitability. Increased neural activity in individuals with migraine (MIG) could be associated with this hyperexcitability. Fractional amplitude of low frequency fluctuations (fALFF) is a functional magnetic resonance imaging (fMRI) measure of spontaneous blood oxygen level-dependent signal which has been linked to disrupted neural processing in various conditions, including migraine (Hodkinson et al, 2016). The present study examines Slow 4 (S4, 0.027-0.073Hz) and Slow 5 (S5, 0.010-0.027Hz) fALFF in the thalamus, a key region for nociceptive processing, and their relationship with migraine symptomatology. Sixty-seven MIG and 30 healthy volunteers underwent a 3T resting-state fMRI scan. MIG completed daily diaries tracking migraine attack qualities for 30-days prior to scanning. This included start and stop times, which were used to calculate attack duration. In region-of-interest analyses, MIG demonstrated elevated S4 values in the R and L thalamus (all $p < .05$, $d > .47$), which were correlated with average migraine attack duration (all $p < .05$, $r = 0.38$). Whole-brain, voxel-wise analyses revealed clusters of elevated S4 values in the R thalamus, posterior cingulate gyrus, and precuneus, as well as elevated S5 values in the cerebellum and visual area MT. Values extracted from the R thalamus cluster were positively correlated with average migraine attack duration ($p = .01$, $r = .40$), and MT was positively correlated with migraine frequency ($p = .007$, $r = .33$). Our results indicate that elevated fALFF is associated with clinically relevant aspects of migraine presentation.

Exploring Sex and Gender Differences in Pain Processing: A Pilot Neuroimaging Study of Transgender Men, Cisgender Men, and Cisgender Women

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Many factors influence pain experiences, including social factors associated with gender and biological elements associated with sex (Martin, 2019). The aim of this pilot investigation is to explore potential neural and behavioral patterns in pain processing between transgender and cisgender individuals. Data from 12 participants (4 tran-smen, 4 cis-men, 4 cis-women) who completed a conditioned pain modulation paradigm were included. Self-reported pain scores were used as behavioral pain measures, and Functional Near-Infrared Spectroscopy oxygenated hemoglobin concentration data were used to examine neural activation. Visual analysis of oxygenated hemoglobin concentrations and means were used to determine potential trends between trans-men, cis-men, and cis-women. This analysis showed potential trends suggesting that trans-men may have distinct patterns of activation in the left prefrontal cortex, differing from cis-men and women during initial applications of the test stimulus. Additionally, during the application of test and conditioned stimulus, trans-men may resemble cis-men more closely than cis-women in prefrontal and right somatosensory cortex activation. These findings may suggest that trans and cis men share similar neural pathways and pain-coping mechanisms that could be different than those in cis-women, with trans-men aligning more with their gender identity than their sex assigned at birth. In addition to replication with a larger sample, further research should explore the impact of hormone therapy on these neural responses, whether these patterns correlate with pain tolerance or pain-related anxiety, and how the prefrontal cortex is involved with emotional and cognitive responses to painful stimuli. Funded by National Institutes of Health (R35GM142676-01).

A Longitudinal 1H-Magnetic Resonance Spectroscopy Study of Thalamic Neurometabolite Alterations in Knee Osteoarthritis Patients One Year Post-Total Knee Arthroplasty

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Our previous work using 1H-magnetic resonance spectroscopy (MRS) investigated longitudinal changes of thalamic levels of the neuronal integrity marker N-Acetyl Aspartate (NAA) and the glial marker myo-inositol (mIns) in knee osteoarthritis (KOA) patients undergoing total knee arthroplasty (TKA) from baseline to 4-weeks post-TKA. At baseline, NAA levels were lower in patients compared to healthy controls (HC). NAA levels were normalized by 4-weeks post-TKA. At baseline, mIns was higher in patients compared to controls and increased further by post-TKA (Weerasekera et al., 2021). The purpose of this study was to extend our investigation by scanning the same cohort of KOA patients at one-year post-TKA. Forty-three KOA patients (mean age 66±8 years, 48.8% female) had preoperative, 4-week, and 12-month scans, which employed a PRESS sequence (TE=30ms, TR=1.7s, voxel size=15×15×15mm). Twenty-three HC (mean age 54±16 years, 52.2% female) were scanned once cross-sectionally for comparison. A linear mixed-effects model was applied, regressing metabolite levels on time (preoperative, 4-week, and 12-months) and age. Similar to what we observed at 4-weeks, at 12-months the NAA levels in patients continued to remain normalized, not differing significantly from those in HCs ($p > 0.05$). In contrast, mIns levels remained slightly elevated compared to HCs (p's < 0.01), similar

to what was observed at 4-weeks, but with significant decrease toward HC levels, compared to the baseline and 4-week scans. These results highlight the differential time course of neuronal and glial markers in response to TKA, and suggest reversibility of central nervous system alterations associated with KOA following surgery.

Investigation Of Intensity Dependent Behavioral, Neural, And Autonomic Interactions During Tonic Pain

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Pain involves a complex interplay between neural and autonomic activity during the anticipation, duration, and recovery periods of noxious stimuli, yet few studies have comprehensively investigated how these signals interact in these timeframes to produce the pain experience. In an ongoing study, healthy subjects (N=68) underwent a cold pressor test (CPT) to their left foot while recording 32-channel electroencephalogram (EEG), electrocardiogram, electrodermal activity (EDA), respiration, and continuous blood pressure. The CPT was performed at three stimulus intensities: room temperature (20-22 C), cold (10-12 C), and very cold (0-2 C). After a 1-minute anticipation period, subjects submerged their foot for a 2-minute CPT followed by a 2-minute recovery while continuously rating their pain intensity on a 0-10 sliding scale ranging from “no pain” to “worst pain imaginable.” The first 10 subjects (6F/4M) demonstrate intensity-dependent increases in pain ratings, heart rate, and systolic blood pressure, but not EDA or respiration. Mean +/- standard deviation (std) pain ratings (0-10) during the CPT for room temperature, cold, and very cold trials are 0.45 +/- 0.55, 3.43 +/- 2.59, and 5.86 +/- 2.40, respectively. Mean +/- std heart rate changes from baseline are: -3.04 +/- 5.96, 1.54 +/- 6.86, and 9.66 +/- 9.11 bpm. Mean +/- std systolic blood pressure changes from baseline are 7.89 +/- 9.81, 10.32 +/- 9.32, and 16.48 +/- 10.80 mmHg. Preliminary analysis reveals the CPT produces intensity-dependent behavioral and cardiovascular autonomic responses. Next steps include continued recruitment and analysis of EEG-autonomic interactions during each CPT stage (anticipation, stimulus, recovery). Start-up funding from the Fralin Biomedical Research Institute.

Modulation in Resting Beta Power Due to Pain Not Fear of Movement

Rachel Ho, Jinhan Park, Wei-en Wang, Stephen Coombes; University of Florida

Modulation in Resting Beta Power due to Pain not Fear of MovementDepartment of Applied Physiology and Kinesiology, University of FloridaPain can lead to profound adaptations in behavior that resemble fear of movement. While several studies have investigated behavioral changes in individuals with cLBP and fear of movement compared to healthy controls, a few studies have investigated the neural circuitry that underlies this relationship. The overall goal of this study was to use source analysis while controlling for the aperiodic component to determine whether fear of movement in cLBP is associated with altered power in beta and alpha bands at rest compared to healthy controls. A total of 95 individuals participated in this study. Seventy individuals had cLBP and twenty-five were sex and age-matched healthy controls. We used a TSK median split to divide the seventy individuals with cLBP into two groups: 39 people in the low fear group and 31 people in the high fear group. There were no significant differences to

report between groups when comparing raw alpha power, raw beta power, and periodic alpha power. However, after correcting for the aperiodic component we found a difference between the controls and high fear and the controls and low fear groups in periodic beta power. Specifically, the individuals with cLBP had attenuated beta power compared to controls. There were no significant differences between the low and high fear of movement groups, suggesting that fear of movement does not seem to be associated with changes in beta power.

Nociceptive Experiences Increase Somatosensory Gating Of Innocuous Stimuli: A Magnetoencephalography Study

Mahak Virlley, Lin Guo, Megan White, Tyrell Pruitt, Una Makris, Jason Zafereo, Amil Shah, Frank Yu, Joseph Maldjian, Amy Proskovec; University of Texas Southwestern Medical Center

Nociception involves a dynamic integration of sensory and contextual processes through the collaboration of multiple brain regions, including the primary somatosensory cortex (SI) and limbic regions (Garcia-Larrea 2013). Similar to noxious stimuli, innocuous stimuli induce robust increases in gamma-band neuronal oscillations in contralateral SI (Rossiter 2017). In healthy individuals, these SI gamma responses exhibit somatosensory gating (SG), whereby the response to the second stimulus in a pair is attenuated (Spooner 2019). SG is thought to measure preattentive sensory inhibition. However, sensory inhibitory processing in individuals with moderate-to-severe nociceptive pain (MSNP) has not been interrogated using SG. We predict that individuals with MSNP will exhibit SG in additional regions beyond SI. We acquired noninvasive magnetoencephalography (MEG) neuroimaging on 28 adults with MSNP (M age = 66.5, 17 female) and 43 no-pain controls (M age = 63, 28 female) during a somatosensory paired-pulse paradigm. All MEG data underwent standard preprocessing and significant gamma oscillatory responses relative to baseline were imaged using a beamformer. The resulting whole brain maps were used to create gating difference (GD=Stimulus 1-Stimulus 2) maps per subject. GD maps were subjected to an ANCOVA, with pain group as a between-subjects factor while controlling for education level, depression and anxiety scores, and results were corrected for multiple comparisons. Significant group differences were observed in bilateral thalami, such that individuals with MSNP demonstrated SG in these regions, whereas controls did not ($p<0.01$, corrected). As hypothesized, additional limbic regions showed gating in MSNP, possibly reflecting overactive bottom-up sensory inhibition.

Associations Between Pain Experiences and Gray Matter Volume in Youth in the Adolescent Brain Cognitive Development (ABCD) Study

Carmen Bango, Scott Jones, Sara Shao, Dani Del Rubin, Arturo Lopez Flores, Bonnie Nagel, Amy Holley, Anna Wilson; Oregon Health & Science University

Pain in youth is a growing public health concern with increased risk for anxiety, depression, and disability in adulthood. While research suggests pervasive differences in brain morphology with pain in adults, this relationship is not yet well-characterized in adolescence. To address this gap, we conducted exploratory analyses examining pain-related associations with gray matter volume

across 68 cortical and 14 subcortical regions in a community sample of 7,719 children (mean age=11.96; 47% female at-birth) from the Adolescent Brain Cognitive Development (ABCD) study. Using linear mixed-effects models adjusted for age, sex at birth, annual family income, intracranial volume, and family-specific random effects, we examined 1) structural differences between children with and without past-month pain and 2) associations with a continuous latent pain severity factor comprising measures of average pain, worst pain, pain limitations, and daily pain duration, in those reporting past-month pain (n=2,675). Results showed no significant morphological differences between groups with and without past-month pain. However, among participants reporting pain, higher scores on the latent pain factor were associated with lower gray matter volume in five cortical areas: bilateral precentral gyrus, right postcentral gyrus, right inferior parietal gyrus, and left lateral occipital gyrus (all $p_{fdr} < 0.05$). These findings suggest neurostructural factors in predominantly sensorimotor regions are related to pain severity in adolescents, potentially reflecting patterns of robust early development or accelerated pruning in these areas associated with heightened pain experiences. Next steps involve examining biopsychosocial mediators and using a longitudinal approach to clarify the temporal nature of these findings.

Expectation Violations Result In FC Changes With dACC Based on Cue: A PPI Analysis
Rahwa Netsanet, Joshua Brown; Indiana University Bloomington

The purpose of this study is to assess whether whole-brain functional connectivity (FC) with the dACC differs during anticipation and stimulation phases based on expectancy. A psychophysiological interaction (PPI) analysis was performed on data from 26 healthy subjects who underwent a cue-target shock paradigm, where a cue presented during anticipation was either matched (high cue/high shock) or mismatched (high/low). Previous research found the dACC was responsive to aversive stimulation; thus, a 5mm spherical region around the peak activation was used as the seed region. Analysis of cue effects during anticipation and stimulation showed no difference between the high cue and low cue conditions ($p>0.05$), indicating that the expected shock level alone does not produce significant FC with the dACC. Further analysis revealed that mismatched trials (surprisingly high/low shocks) elicited increased FC between the dACC and the OFC ($p<0.05$, cluster corrected). Post-hoc tests into which surprising condition (surprisingly high or surprisingly low) may be driving this effect showed no significant FC in surprisingly high shock conditions (low/high), but the surprisingly low shock condition (high/low) showed increased FC with the dACC in the calcarine and precuneus ($ps<0.001$), and decreased FC with the right mid frontal gyrus and right supramarginal gyrus ($ps<0.001$). This suggests that surprisingly low shocks engage regions involved in visual processing and self-referential thought while reducing FC with regions implicated in executive function and attention, potentially reflecting relief following heightened vigilance. These findings highlight the significant role of expectation violation (surprise) in processing aversive cues and stimuli, warranting further inquiry.

Effects of Green Light Exposure on Pain-like Behavior and Periaqueductal Gray Connectivity in a Rodent Model of Knee Osteoarthritis

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University of Maryland Baltimore

Functional changes in pain-processing brain regions have been observed across various chronic pain conditions, including persistent pain related to knee OA, which disproportionately affects women. Our previous investigation demonstrated that green light exposure with green light-emitting diodes (GLED) reduces primary hyperalgesia in a sex-dependent manner in the monoiodoacetate (MIA) model of knee OA. Preclinical studies have demonstrated that green light analgesia can be partly attributed to modulation of the pain-processing neuraxis. However, no studies have investigated the effects of GLED exposure on brain functional connectivity (FC) in a model of chronic pain using both sexes. Here, we examined the effects of GLED exposure on pain-like behavior and periaqueductal gray connectivity in the MIA model of knee OA using the static weight bearing test and functional MRI (fMRI), respectively. GLED exposure attenuated weight bearing asymmetry induced by unilateral injection of MIA (3mg/15μL) in the left knee joint compared to ambient room light (ARL) controls, with analgesic effects occurring sooner in males. fMRI data acquired 30-31 days after injection revealed greater PAG FC with the rostral anterior cingulate cortex (rACC), insula, and primary somatosensory cortex in GLED-exposed rats. Additionally, greater PAG FC with the rACC, prelimbic cortex, motor cortices, and insula was observed in GLED-exposed males compared to their female counterparts. These results demonstrate that GLED elicits analgesia and alters PAG FC in a sex-dependent manner in the MIA model of knee OA. These findings warrant future investigation into the effects of GLED on PAG-based descending pain inhibition in both sexes.

Machine Learning Approach for Pain Intensity Classification with Structural Neuroimaging Data: A Preliminary Study

Behnaz Jarrahi; Stanford University School of Medicine

Objectively quantifying pain remains a challenge in the clinical field. Leveraging recent advancements in neuroimaging and machine learning (ML), this study aimed to classify pain intensity by applying ML and identifying key neuroanatomical features using the Human Connectome Project (HCP) S1200 dataset (n = 951). The NIH Toolbox Pain Intensity Survey score was used to categorize participants into high and low pain groups, while the Adaptive Synthetic Sampling (ADASYN) algorithm addressed class imbalance. Brain features, including cortical and subcortical thickness, volume, surface area, curvature, and folding index, were extracted from the structural MRI data using the HCP FreeSurfer pipeline. The dataset was divided into training and testing sets (80:20 split). The nested 5-fold cross-validation method was utilized. Fifteen ML classifiers from the Scikit-learn library were evaluated based on testing accuracy, precision, recall, F1-score, and area under the ROC curve score. The top-performing models were the Extra Trees Classifier, Random Forest Classifier, LGBM Classifier, and XGB Classifier, with testing accuracy, recall, and F1 all above 90%. The SHAP (SHapley Additive exPlanations) method was used to determine significant morphological features associated with pain intensity. Preliminary findings indicate that features related to the cognitive control and somatomotor systems contribute the most to pain intensity classification. Key regions include the frontal pole, parahippocampal area, inferior frontal and inferior parietal regions, medial orbitofrontal cortex, paracentral lobule, and lateral occipital cortex. These preliminary results

underscore the potential of ML and neuroimaging to yield objective measures of pain that can advance the field of personalized medicine. Funding: K25DA048179.

Cortical Activity Measured by Functional Near-Infrared Spectroscopy in Low Back Pain: A Systematic Review

Jie Chen, Meghan Poe, Tingting Liu, Param Patel, Huan Kuang, Aokun Chen, Yang Wang, Jennifer Dungan, Angela Starkweather; Florida State University

This systematic review aimed to summarize knowledge regarding brain activation patterns during noxious stimuli and non-noxious tasks measured by functional near-infrared spectroscopy (fNIRS) in patients with low back pain (LBP). Journal articles published in English were identified in electronic databases, including CINAHL, PubMed, PsycINFO, Scopus, and ISI Web of Science from the earliest dates to August 2024. Unpublished studies were searched in clinical trial registrations, Google Scholar, ProQuest Dissertations, and Theses Database. The following keywords were combined in the search strategy: (1) cortical activity, (2) fNIRS, and (3) back pain. Two reviewers independently reviewed 330 publications and agreed on ten studies that met eligibility for inclusion in this review. Three studies described or compared differences in cortical activity during noxious and non-noxious stimuli on the low back between subjects with LBP and healthy controls (HCs). Three studies compared postural/standing tasks evoked cortical activity among subjects with LBP. Four studies investigated the pain management interventional effects on LBP relief associated with changes in cortical activity. The results supported that patients with LBP have increased activation in the dorsolateral prefrontal cortex and supplementary motor area compared to HCs, and decreased cortical activities in these brain regions are associated with LBP relief after the interventions. Growing evidence supports the potential of fNIRS in capturing the altered cortical activity related to LBP. Further research is needed to evaluate these findings comprehensively and determine the clinical potential of fNIRS as a standard care modality for LBP management.

Knee pain may affect glymphatic integrity in deep white matter via sleep impairment effects

Pedro Valdes-Hernandez, Soamy Montesino-Goicolea, Chavier Laffitte Nodarse, Alisa Johnson, Roger Fillingim, Yenisel Cruz-Almeida; University of Florida

Previous research implicates the brain in the bidirectional pain-sleep associations, and sleep plays a critical role in brain health where sleep disturbances disrupt glymphatic clearance. No studies to date have examined how pain may contribute to glymphatic dysfunction in persons with knee osteoarthritis pain. As part of a larger longitudinal study, we tested two models temporally relating pain severity and glymphatic system (GS) integrity in deep white matter, accounting for sleep quality. We hypothesized that 1) variations in chronic pain severity would influence future changes in GS integrity, irrespective of sleep quality changes; 2) variations in chronic pain severity would influence future changes in GS integrity, mediated by sleep quality changes; and 3) initial variations in sleep quality would influence future changes in chronic pain severity through modifications in GS integrity. Participants experiencing functionally limiting or high impact knee pain (n=87) completed self-reported measures of pain, sleep impairment, and

underwent an MRI to obtain a surrogate of GS integrity in deep white matter at baseline and two years later. Only hypothesis 2 was supported, where widespread pain and longer pain durations at baseline significantly influenced a decrease in the GS integrity of the left hemisphere through increases in sleep impairment two years later (corrected p=0.039). Future research is needed on the bidirectional connection between chronic pain and sleep quality in the context of brain health.NIH/NIA Grants K01AG083228 (PAVH); R01AG059809, R01AG067757 (YCA); R37AG033906 (RBF); and T32AG049673 (SMG). A portion of this work was performed in the McKnight Brain Institute at the National High Magnetic Field Laboratory's Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) Facility, which is supported by National Science Foundation Cooperative Agreement No. DMR-1157490 and DMR-1644779 and the State of Florida.

Brain and Spinal Cord Correlates of Deficient Endogenous Pain Modulation in Fibromyalgia Identified by Corticospinal Functional Magnetic Resonance Imaging
Dario Pfyffer, Merve Kaptan, Christine SW Law, Kenneth A Weber II, Valeria Oliva, Sandrine Bédard, Teresa Indriolo, Tara Maronesy, Gary H Glover, Sean Mackey; Stanford University School of Medicine

Chronic widespread pain represents the cardinal symptom of fibromyalgia (FM). While dysfunctions in the endogenous pain-modulatory system are known to contribute to pain, information on specific mechanisms and affected brain/spinal cord (SC) areas and their interaction is limited. This study aimed to characterize corticospinal correlates of deficient descending pain modulation in FM, by means of combined brain-SC functional magnetic resonance imaging. Inspired by experimental pain-relieving effects reported for physical therapy/non-invasive neurostimulation of executive cortical regions, we here used a design pairing right-hand gripping with noxious heat stimulations. We scanned 41 females (20 FM, aged 22-65; 21 healthy volunteers [HV], aged 21-62) at 3T (GE Discovery 750) using an echo-planar imaging pulse sequence (repetition time=2.5s/echo time=30ms/GRAPPA=2) with 30 brain and 13 cervical SC (centered at C6) slices. The experimental design included four conditions (8x each, 13s), randomized: stimulation ON/OFF x gripping ON/OFF. Thermal stimuli were applied at right volar forearm (C6 dermatome) at individualized temperatures (6/10, ATS thermode [Medoc]). Repetitive isometric right-hand gripping by hand dynamometer (60% of maximal voluntary contraction [BIOPAC]). We demonstrated elevated activation in pain-modulatory brain areas (i.e., prefrontal/primary motor cortex) during combined stimulation-gripping in HV versus FM, paralleled by lower pain ratings, and, in turn, increased nociceptive signaling in SC dorsal horns in FM versus HV. Identification of dysfunctional endogenous pain modulation networks along the neuroaxis might present promising neural targets for more efficient treatment of chronic pain (e.g., non-invasive brain/SC stimulation) and advance the development of pain biomarkers and precision medicine. NIH (R01 NS109450), SNSF (P500PM_214211).

Assessing Functional Connectivity Between Brain and Spinal Cord During Thermal Pain
Merve Kaptan, Dario Pfyffer, Christine S.W. Law, Kenneth A. Weber, Gary Glover, Sean Mackey; Stanford University School of Medicine

The dorsal horn is critical in pain processing, serving as the first synaptic site in the afferent pathway and a key target for descending modulation. While non-invasive spinal imaging has advanced, understanding the interactions between the brain and spinal cord during pain processing remains limited. This study addresses this gap by examining functional connectivity (FC) between the brain and spinal cord during painful heat stimulation in a pain-free sample (28F) by using a corticospinal fMRI protocol. Thermal stimuli were applied to the forearm at three intensities (46°C, 47°C, and 48°C), and ratings were recorded. Brain and spinal cord data were processed with standard steps, and seed-based FC (using the right dorsal horn at C5-C7 levels as seed) analysis was used to assess functional connectivity between the spinal cord and brain. Results showed positive correlations between the spinal cord and brain regions involved in pain processing: thalamus, supplementary motor area, anterior cingulate cortex, precuneus cortex, and medial prefrontal cortex. Importantly, the strength of connectivity between the dorsal horn and the brainstem, insula, superior temporal gyri, and cingulate cortex was significantly correlated with individual pain ratings, highlighting the functional importance of these connections in pain modulation. Understanding corticospinal functional connectivity during pain can enhance our knowledge of pain modulation. Insights into how the brain and spinal cord interact during pain can reveal why pain modulation fails in chronic pain conditions like fibromyalgia which may guide targeted therapies that restore balance in these networks and personalize treatment approaches for patients with chronic pain.(R01NS109450).

Lower Positive Coping Is Associated With Higher Movement-Evoked Pain Among Adults With Low Back Pain

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Low back pain (LBP) affects over 577 million people worldwide and is a leading contributor to global disability. Therefore, a greater understanding of how psychological and movement systems work together to drive LBP-related functional impairments is needed. This cross-sectional, secondary analysis of seventy-two adults with LBP (mean age=45 years; 38 females, 34 males) evaluates the novel relationship between movement-evoked pain (MEP) and positive psychological coping factors, including pain self-efficacy (PSEQ) and self-efficacy for rehabilitation (SER). Participants completed the Optimal Screening for Prediction of Referral and Outcome-Yellow Flag questionnaire to determine PSEQ and SER scores. Participants' average MEP was measured during walking tasks (e.g., fast-walking, Timed-Up-and-Go) and Back Performance Scale (BPS) tasks (e.g., box lift, supine to sit). MEP was recorded during each task using a Numeric Pain Rating Scale. Separate hierarchical regression models were generated with age and sex added as predictors in step 1 and positive coping added in step 2 (either PSEQ or SER scores); MEP measures served as dependent variables. Across all models, sex and age were not significant predictors ($p>0.05$). For PSEQ models, PSEQ predicted MEP during walking (beta= -0.42, $p<0.001$) and MEP during BPS tasks (beta= -0.39, $p=0.001$). For SER models, SER predicted MEP during walking (beta= -0.46, $p<0.001$) and MEP during BPS tasks (beta= -0.43, $p<0.001$). Findings indicate lower self-efficacy is associated with higher MEP, which could negatively affect function. Concurrent evaluation of LBP-related psychological and movement factors may help clinicians better understand patients' potential for functional recovery and/or risk for future disability.

Pain, Movement, and Rehabilitation Science

People With Acute Low Back Pain Display Impaired Spinal Movement During a Functional Activity Similar to People with Chronic LBP

Linda R. van Dillen, Christopher Peterson, Vanessa M. Lanier; Washington University Medical School

People With Acute Low Back Pain Display Impaired Spinal Movement During a Functional Activity Similar to People with Chronic LBP Linda R. van Dillen, Chris M. Peterson, Vanessa M. Lanier; Program in Physical Therapy and Department of Orthopaedic Surgery, Washington University Medical SchoolSpinal movement impairments (SMIs) are characterized by the lumbar spine moving more readily than other joints that contribute to attaining a movement goal. SMIs are important to the clinical presentation of chronic low back pain (LBP). Treatment to remediate SMIs during functional activities results in short- and long-term improvement in LBP and LBP-related disability (van Dillen, 2021). Thus, it would be important to know if SMIs are present in people with acute LBP. Our purpose was to examine spinal movement during a representative functional activity test of picking up a light-weight object (PUO) in mid-range of forward bending. We compared lumbar excursion across movement time in people with acute LBP (n=32; age: 35 [9.9]), chronic LBP (n=32; age: 33.8 [10]) and back-healthy people (n=16; age: 32 [9.4]). Overall, people in the acute LBP group displayed a greater magnitude of lumbar excursion in the early phase of the PUO movement, i.e., more impaired, than the chronic LBP group and the back-healthy group. Given the importance of SMIs in people with chronic LBP, our preliminary findings suggest that further examination of SMIs in people with acute LBP is warranted to better understand their potential role in LBP course, in particular, the acute to chronic transition. Funding: R01 HD108240.

High Fitness And Vigorous Physical Activity Relate To Select Pain Sensitivity Assessments In Healthy Adults

Omid Khoshavi, Laura A. Frey Law, Shannon L. Merkle; University of Iowa

Increasingly, research suggests that physical activity (PA) may assist in the prevention of chronic pain and the reduction of both acute and chronic pain symptoms. Yet, the relationships between quantitative sensory testing (QST) of pain processing and PA remain unclear with mixed findings in the literature. This study aimed to investigate associations of multiple measures of PA and fitness assessments with multiple measures of pain sensitivity, where we hypothesized associations with both static and dynamic QST. 64 healthy adults (30 F) spanning both high and low activity levels completed a battery of mechanical static (pressure pain thresholds, PPT) and dynamic (temporal summation, TS, and conditioned pain modulation, CPM) QST. PA was assessed by self-report using the International Physical Activity Questionnaire (IPAQ) and objectively by accelerometry over 7 days: sedentary, moderate-to-vigorous (MVPA), vigorous and total PA. YMCA step test assessed cardiorespiratory fitness. Relationships were assessed using correlation and regression analyses. Higher PPTs were related to greater self-reported MVPA, vigorous PA, total PA, accelerometry vigorous PA, and high cardiorespiratory fitness (p

≤ 0.01). Only self-reported vigorous PA was inversely correlated with TS ($p = 0.01$); no other PA or fitness metrics significantly related with TS or CPM ($p \geq 0.04$). We conclude that not all fitness and PA metrics are equally related to static and dynamic QST. This demonstrates that the mixed findings reported in the literature are also observed in a single cohort, suggesting that PA and fitness show unique associations with different QST assessments, and self-report more than accelerometry.

The Pain Catastrophizing Inventory: Rethinking Trait Assessment of Catastrophizing
Adam Janowski, Omid Khoshavi, Laura Frey Law; University of Iowa

Pain catastrophizing is defined as a negative cognitive response to pain which includes elevated perceived pain severity, feelings of helplessness, and rumination. One commonly used measure is the 13-item Pain Catastrophizing Scale (PCS). However, variability in PCS scores (range: 0-52) may be influenced by each individual's unique imagined pain scenario. The 24-item Pain Catastrophizing Inventory (PCI) was developed to assess catastrophizing to 6 specific painful scenarios of varying pain intensity and quality (range: 0-96). The purpose of this study was to evaluate the PCI as a more controlled measure of trait catastrophizing. We hypothesized that 1) the PCI would be moderately correlated to the PCS but with less between subject variability, 2) each of the PCI scenario subscores would be moderately inter-correlated and associated with their corresponding pain intensity and quality metrics. Data was collected using online surveys from 93 adults (28% reported having experienced chronic pain) which assessed the PCS and PCI. The PCI was significantly correlated with the PCS ($R=0.62$, $p<0.001$), but with reduced variability (coefficients of variation: 23.4% and 30%, respectively). Using mixed models with random slopes and intercepts, PCI scenario subscores were explained by both pain intensity ($\beta=0.30$, $p=0.002$), pain quality ($\beta=-1.28$, $p=0.01$), and their interaction ($\beta=0.97$, $p<0.001$). The PCI, assessing 4 items per scenario, appears to capture trait catastrophizing with overlapping but reduced variance relative to the PCS, using 13 items with an unknown scenario. The level of catastrophizing, measured by the PCI, is strongly associated with a specific scenario's pain intensity and quality.

Noninvasive Brain Stimulation Plus Pain Neuroscience Education in Chronic Low Back Pain: A Pilot Randomized Control Trial
Cory Alcon, Kelli Brizzolara, Hui-Ting Goh, Sharon Wang-Price; High Point University

Priming the neural circuity likely targeted by pain neuroscience education (PNE), using transcranial direct current stimulation (tDCS) may enhance the efficacy of PNE. The aim of this study was to compare the effects of active tDCS + PNE to sham tDCS + PNE on measures of pain, pain behaviors, and cognitive function in participants with chronic low back pain (CLBP) and high pain catastrophizing. 20 participants were recruited and randomly allocated into the active tDCS + PNE (n=10) or sham tDCS + PNE (n=10) groups. All participants received five sessions of their assigned interventions over a 2-week period. The active tDCS + PNE group received 20 min of 2 mA, anodal current applied to the left dorsolateral prefrontal cortex. Within groups, both interventions demonstrated significant improvement in NPRS, PCS, and TSK. The

active tDCS + PNE group also demonstrated significant improvement in the SCWT, CTMT2—Inhibitory, and CTMT2—Set Shifting. Between groups, the active tDCS + PNE group showed significantly greater improvement on the PCS, SCWT, and CTMT2—Inhibitory. The results of this pilot study suggest that active tDCS + PNE appeared to provide greater improvement than sham tDCS + PNE on levels of pain catastrophizing and attentional interference in participants with CLBP and high pain catastrophizing. This presents evidence of a priming effect of transcranial direct current stimulation on pain neuroscience education in participants with CLBP and high pain catastrophizing and supports that the combination of interventions improves pain behavior and cognitive function greater than pain neuroscience education alone.

Perspectives Of Private Practice Physical Therapy Healthcare Systems In A Pragmatic Clinical Trial Fibromyalgia TENS In Physical Therapy (FM-TIPS)

B Van Gorp, Kari Vance, Jonah Pedelty, Elizabeth Johnson, Kristin Archer, Leslie Crofford, Dana Dailey, Carol Vance, Kathleen Sluka, Heather Reisinger; University of Iowa

In the United States, private practice healthcare systems are the largest employers of physical therapists - 43% (Bureau of Labor Statistics, 2023) - many being in rural communities. Fibromyalgia TENS In Physical Therapy Study (FM-TIPS) is a pragmatic clinical trial including 25 clinics in four Midwest private practice systems. This is a qualitative analysis of the perspectives of four participating private practice physical therapy healthcare systems and a comparison of workforce demographics national averages to study trained clinicians. We conducted semi-structured interviews of the four private healthcare systems' directors. Questions were designed by investigators addressing experiences, barriers, benefits, and future research. Four major themes emerged when interview transcriptions were coded and analyzed by the research team: participation is not burdensome; private practice directors see benefits; participation fosters learning, new experiences, and challenges; private practice healthcare systems should work with governing bodies to further research participation. Secondary analysis included surveys to all study clinicians gathering workforce demographics. Compared to national averages from the American Physical Therapy Association (2023) study trained clinicians (n=70) membership was 86%, nationally 19%; residency trained study clinicians 13%, nationally 3% for some workforce comparison results. Private practice physical therapy participation in research is important to translate and implement evidence-based practice. When designed in collaboration with healthcare systems, participation is feasible, provides benefits to the clinics and practitioners and fosters learning. Understanding facilitators and barriers to participation in for-profit healthcare systems can inform future clinical research. This Research is supported by National Institutes of Health Grant UG3/UH3 AR076387.

Relation Of Immune Profile To Exercise-Induced Pain And Fatigue In Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Post-acute Sequelae Of SARS-CoV-2 Infection

Giovanni Berardi, Adam Janowski, Samuel McNally, Gregorius Bernhard, Alpana Garg, Kathleen Sluka; University of Iowa

Individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and post acute sequelae of SARS-CoV-2 infection (PASC) experience exercise-induced pain and fatigue (EIPF). EIPF can occur during and after exercise and is a barrier to participation in daily activities and exercise. While mechanisms of pain and fatigue are likely multifactorial, several studies suggest a prominent role of the immune system. This study examined pain, fatigue, and immune cell profiles before and after an exercise task in 30 individuals with PASC, ME/CFS, and controls. Pain and fatigue were assessed prior to and for 7-days following exercise using 0-10 numerical rating scales. PBMCs were isolated and monocyte, T-cell, natural killer cell, and B-cell phenotypes were characterized using flow cytometry before and after exercise. EIPF was defined as a composite change score for pain and fatigue over 72-hours following exercise and ranged from -4.0-5.3/10 in individuals with ME/CFS and PASC. There were no differences in monocyte, T-cell, natural killer cell, or B-cell phenotypes at baseline or changes in phenotype following exercise among groups ($p>.05$). Cluster analysis identified two distinct groups based on the baseline monocyte phenotype, an inflammatory group (classical monocytes>non-classical monocytes) and a non-inflammatory group (classical monocytes

Don't Judge Me: Relationships Between Fear of Pain and Anxiety with Perceived Exertion and Pain During Isometric Exercise in Youth with Chronic Pain

Kimberly Brown, Nina Linneman, Ke Yan, Rachel Schmidt, Steven Weisman, Keri Hainsworth; Medical College of Wisconsin

Physical activity is often prescribed for treatment of pediatric chronic pain. Yet for these youth, barriers to engaging in activity exist. The purpose of this study was to examine if fear of pain or anxiety, factors known to influence physical activity and pain recovery, are associated with ratings of perceived exertion and pain during exercise. We also evaluated differences between groups varying in presence/absence of chronic pain and obesity: healthy controls (HC), obesity alone (O), chronic pain alone (CP), and chronic pain with obesity (CPO). Adolescents (n = 157, 13-17 years, 51% female, 85% White) completed the Fear of Pain Questionnaire (FOPQ) and the Screen for Child Anxiety Related Disorders (SCARED) prior to engaging in isometric exercise (3-minute yoga pose). While holding the pose, participants reported their perceived exertion and pain intensity. Across groups, FOPQ was associated with both perceived exertion and pain (p-values<0.001), whereas anxiety was not. Notably, only in the CPO group were several anxiety subscales associated with perceived exertion and pain. Specifically, separation anxiety and school avoidance subscales were associated with higher perceived exertion and pain (separation anxiety: p=0.006, p=0.003, respectively; school avoidance: p=0.039, p=0.049, respectively). Additionally, youth with CPO and elevated social anxiety reported higher perceived exertion (p=0.047) than those with scores below a clinical cut-off. These findings show that fear of pain and subtypes of anxiety should be considered when including physical activity in pain management. Additionally, these data identify important psychosocial support needs for youth with CPO as they start to increase physical activity.

The Impact Of Acute Cognitive Stress In Individuals With Chronic Ankle Instability
Elisabeth Ohrnberger, Kyle Kosik, Phillip Gribble; University of Kentucky

The purpose of this study was to compare the stress response associated with an acute cognitive stress test between individuals with chronic ankle instability (CAI) who do and do not self-report chronic ankle pain. A case-control study design was used to enroll 32 volunteers with CAI as defined by the International Ankle Consortium guidelines. Participants were further classified as having chronic pain (n=15) based on the International Association for the Study of Pain criteria. The Montreal Imaging Stress Task (MIST) was used to induce an acute cognitive stress and participants' heart rate was recorded using a Polar Chest Strap and the Elite HRV app. Each participants' stress response during the MIST and during the resting period was quantified by calculating heart rate variable (HRV) outcomes (e.g., time-domain, frequency-domain, nonlinear measures) via Kubios Scientific software. A linear repeated measures model assuming an autoregressive correlation structure was fit for each outcome controlling for sex and pain status. Contrasts between the MIST and during the resting period were built to test for differences. Significance was set a priori as $p \leq 0.05$. Observed results (7/12 HRV outcomes) demonstrated the MIST induced an acute cognitive stress response among all participants, regardless of their pain status ($p<0.05$). Between group analyses suggested that those with painful CAI tended to demonstrate a greater stress response (8/12 HRV outcomes) compared to those without pain, however, these findings were not statistically significant ($p>0.05$). Individuals with CAI experience similar stress responses during the MIST, regardless of ankle pain status.

Exploring Sesnsorimotor Dysfunction in Fibromyalgia: Effect on Pain Sensitivity, Flexibility and Cortical Excitability
Aasheesh Kumar, Uma Kumar, Akanksha Singh, Srikumar Venkataraman, Renu Bhatia; All India Institute of Medical Sciences

Background - Fibromyalgia is a widespread pain condition with neurological distress and sleep impairments. Till date there is no permanent treatment available. Objective evidence for pain interferes with muscular performance and higher center is missing from literature. Aim of the current study was to explore musculoskeletal activity, pain profile and cortical excitability in fibromyalgia patients and compare it with the outcome measures in healthy controls.Methods - Cross-sectional comparative study conducted in 180 participants. Pain was assessed both subjectively and objectively in fibromyalgia patients using visual analogue scale, catastrophizing scale and quantitative sensory testing. Sleep and quality of life were also assessed in patients and controls. Serum level of pain related biomarkers such as beta-endorphins, cortisol, glutamate, serotonin and substance-P were quantified. Moreover, corticomotor excitability was assessed using Transcranial Magnetic Stimulation in healthy controls and fibromyalgia patients.Results - A significant impairment in sleep and quality of life was found in fibromyalgia patients (sleep score = 13.37±0.40) as compared to healthy controls (Sleep score = 4.86±0.29); $p<0.001$. Elevated serum levels of pain and stress biomarkers were evident in fibromyalgia patients. Pressure pain thresholds also favored hyperalgesia and allodynia due to chronic pain (patients = ~140kPa; controls = ~240kPa). Resultant musculoskeletal performance tested using various techniques revealed poor flexibility and range of motion due to pain. Cortical excitability in

fibromyalgia patients were reported significantly higher and altered in fibromyalgia patients.Conclusion - Fibromyalgia pain negatively affects flexibility and cortical excitability resulting in aberred nociception, poor quality of life and sleep.

Impact of Pain History on Outcomes from a 10-Week Veteran Activity Challenge
Victor Schneider, Carly Green, Sharyl Frensemeier; Cincinnati Veterans Affairs Medical Center

Physical activity has been shown to improve general health, disease risk, and progression of chronic illnesses including pain and related conditions (Ambrose & Golightly, 2016). To increase activity, Veterans at Cincinnati VA MC were encouraged to track steps over ten weeks in novel competition between branches of military service ("6-Service Challenge"). Veterans completed an orientation where they received a movement measurement device (e.g., Fitbit) followed by weekly optional group check-ins to review steps and receive psychoeducation on Whole Health programming (e.g., Nutrition). Measures of physical/mental health were collected from medical charts before and after the challenge. We recruited 68 predominately older, white male-identifying, not-Hispanic or Latino (Mage=61.00±11.91yrs, 22.1% female-identifying; 26.5% Black or African American; 1.5% Hispanic/Latino) Veterans with significant chronic pain history (70.6% 1+ chronic pain or related conditions). Average weekly steps were calculated if a Veteran tracked 5 out of 7 (>70%) days. Veterans reported an average of 8086 steps per week with a significant average increase of 167 steps per week, controlling for age and sex (R^2=.0502, $F_{3,631}$=12.16, p<.001). Preliminary results found a significant interaction between pain history and average percent change in steps over the challenge such that Veterans with chronic pain history reported a smaller percent increase in steps, controlling for age (R^2=.0805, $F_{2,65}$=3.931, p=.024). No significant impact was found of challenge participation on physical/mental health. Results suggest Veterans with pain history may benefit from targeted support when participating in activity challenges. Future studies should explore population disparities and more inclusive activity measurements (e.g., calories burned).

Examination of Pain Related Confidence, Knowledge, and Beliefs of Physical Therapy Clinical Instructors
Christopher Covert, Rebecca Greenwood, Steven Lesh; University of Charleston

Clinical instructors (CIs) play a vital role in physical therapy (PT) education supervising students learning to manage patients presenting with persistent pain. Historically, pain science was not covered well during PT education. The purpose of this study was to investigate if the number of hours of pain science continuing education (PSCE) influenced PT CI's confidence, knowledge and beliefs related to the clinical management of patients presenting with persistent pain. The investigators surveyed CIs through convenience sampling utilizing social media and email inviting each to participate. The survey included questions regarding demographic information, amount of PSCE, pain science knowledge, beliefs related to persistent pain (HC-PAIRS), and confidence in managing patients with persistent pain. A Mann-Whitney-U was utilized for statistical analysis comparing confidence, beliefs, and knowledge based on how many hours of PSCE completed (10 or less vs. 11+). A total of 44 responses were received for data analysis. CIs completing 11+ hours had significantly improved knowledge (p=0.047), confidence (p<0.001),

and beliefs (p =0.021) related to managing persistent pain. There were no significant differences related to the year of graduation from entry-level DPT program, age of the clinical instructor, or practicing in a rural vs. urban area. On average, CIs reported that pain science content was not covered well (4.39) in their entry-level education (1=no coverage,10=excellent coverage). CIs serve a crucial role in mentoring future physical therapists in the management of patients with persistent pain, emphasizing the importance of contemporary PSCE.

Older Adults with Knee Osteoarthritis Exhibit Accelerated 'Gait Age': A Preliminary Machine Learning Approach

Ania Lipat, Pedro Valdes-Hernandez, Yenisel Cruz-Almeida; University of Florida

Assessing the difference between an individual's chronological age and age predicted from physiological measures has helped identify individuals experiencing accelerated aging. This approach, however, has yet to be applied to gait performance, which is easily measured, closely associated with health in older adults, and impaired by pain conditions, such as knee osteoarthritis. This study aimed to evaluate the accuracy of a machine learning model in predicting age based on gait performance (i.e., 'gait age') and compare mean gait-predicted age differences between older adults with knee osteoarthritis (N = 10, Mean Age = 73.70 years) and those without chronic pain (N = 26, Mean Age = 72.61 years). Spatiotemporal gait data from healthy older adults (N = 102, Mean Age = 75.43 years) obtained using a GAITRite mat were used as features to train machine learning algorithms to predict age. Among these models, an XGBoost model yielded the best performance (Mean Absolute Error (MAE) = 3.81 years, Mean Absolute Percentage Error = 5.30%). This model was then deployed to predict age using the GAITRite data from older adults with knee osteoarthritis (MAE = 9.25 years) and no pain controls (MAE = 6.41 years). In conclusion, our preliminary machine learning model predicted age with accuracy comparable to existing methods and showed that older adults with knee osteoarthritis exhibited accelerated 'gait age' compared to those without chronic pain. This work introduces 'gait age' as a potential novel biomarker for disease, paving the way for new diagnostic and prognostic approaches.

Examining the Disconnect: A Secondary Analysis of Self-Reported and Objective Physical Activity in a Mind-Body Intervention

John Burns, Jonathan Greenberg, Ana-Maria Vranceanu, Robert Parker, Tamara Somers, Latrice Yates; Rush University Medical Center

Evidence suggests that self-reported and objective measures of physical activity are weakly associated, potentially reflecting different constructs of physical activity. These findings hint at the existence of subgroups exhibiting distinct patterns of variability across self-reported and objective activity. For instance, it is not clear whether individuals with low self-reported/low objective activity can be distinguished from those with low self-reported but high objective activity based on demographic or psychosocial factors. Secondary analyses were conducted with data from an RCT comparing a CBT-based activity intervention to a health education control (10 weeks; n=84). Analyses collapsed across condition. Pre-post change scores on WHODAS (self-report activity) and step count (objective activity with actigraphy) were computed, and the

correlation between these changes was modest (r= -.34). Median splits of WHODAS and step count change scores were calculated. A series of 2x2 ANOVAs were conducted with low/high WHODAS change groups and low/high step count change groups as the IVs and baseline demographic and psychosocial measures (eg, pain catastrophizing) as the DVs. WHODAS x step count interactions were all nonsignificant (F's < 1). Results suggest that 1) people who report change in physical activity during an intervention tend not to be the same people who exhibit change in physical activity; 2) self-reports and objective assessments of physical activity change may not reflect the same phenomena; 3) both self-report and objective measures are critical to provide comprehensive understanding of clinical responses; 4) it remains unclear what factors predict variability across self-report and objective activity assessments. Funding: ORA# 20042413.

Practice Patterns of Physical Therapy Clinical Instructors based on Pain Science Continuing Education

Rebecca Greenwood, Christopher Covert, Steven Lesh; University of Charleston

Physical therapy (PT) is one of the most common interventions for individuals with chronic pain. It is unknown which interventions based in contemporary evidence that clinical instructors (CIs) are using when treating individuals with chronic pain. The purpose of this study is to explore practice patterns of CIs. The researchers surveyed CIs through convenience sampling utilizing social media and email inviting each to participate. The survey included demographic information, amount of pain science continuing education (PSCE), and PT interventions frequency of use via a Likert scale (1-never to 5-always). A Mann-Whitney-U was used to compare CIs with 10 or less hours of PSCE (n=29) and those with 10+ hours (n=15). When asked how well pain science was covered in their entry level program from 1 (none) to 10 (very thorough), CIs reported it was not covered well (M=4.27). The most frequently used interventions were resistance training (M=4.39) and aerobic exercise (M=4.18,). The least frequently used were acceptance/commitment training (M=1.5) and graphesthesia/2-point discrimination (M=1.86). There were significant differences based on amount of PSCE for pain neuroscience education (p<.001), breathing techniques (p=.007), mindfulness (p<.001), graded exposure (p<.001), motivational interviewing (p<.001), graphesthesia/2-point discrimination (p=.036), and neurodynamic interventions (p=.023). There were no differences in use of electrical modalities, manual therapy, mirror therapy, aerobic exercises, resistance training, or acceptance/commitment training. With most CIs reporting pain science wasn't covered well in their entry level program, it is important for practicing therapists to get PSCE to stay aligned with current evidence when treating individuals with chronic pain.

A Comparison Between a Foot Intrinsic Rehabilitation Exercise Protocol and the Standard of Care on Pain Intensity Levels Among Participants with Chronic Ankle Instability: A Multi-Site Randomized Control Trial

Kyle B. Kosik, John J. Fraser, Jay Hertel, Pinata Sessoms, Brian Green, Nicole McCloughan, Dana Golden, Jen Xu, Dante Goss, Phillip Gribble, Danielle M. Torp, Johanna Hoch, Amy Slider, Eliot Hu, Matthew C. Hoch; University of Kentucky

Approximately 40-79% of civilians and active duty service members with chronic ankle instability (CAI) experience persistent pain that limits activities and participating in social function, including occupational requirements. The purpose of this study was to compare the immediate changes in ankle pain intensity levels after a 6-week foot intensive rehabilitation (FIRE) program and standard of care (SOC) treatment for individuals with CAI. A total of 117 civilians (n=77) and active duty service members (n=40) with self-reported CAI were randomly allocated to either the SOC (n=57; age=25.6±7.0years; height: 172.5±9.9cm; weight: 79.8±18.4kg) or the FIRE (n=60; age=26.8±7.0years; height: 173.5±10.4cm; weight: 79.0±17.9kg) program. Participants allocated to the SOC group completed a 6-week protocol focused on ankle strengthening, balance, and range of motion. Participants assigned to the FIRE program completed the SOC protocol plus intrinsic foot strengthening exercises, dynamic foot stability, and plantar massage. Ankle pain intensity levels were assessed at baseline and immediately after the 6-week interventions using the 4 Likert Scale items on Foot and Ankle Disability Index Pain subscale. Higher scores represent less pain intensity levels. A group-by-time repeated-measures analysis of variance demonstrated a significant time main effect ($p<0.001$) that suggested pain intensity levels were lower (baseline: 83.8±14.3% vs post:89.5±13.4%) after the 6-week intervention, regardless of group. No group-by-time interaction or group main effects were observed. Physical rehabilitation can reduce pain intensity levels for patients with CAI. However, the addition of foot focused interventions did not appear to generate greater reductions in pain intensity. Funded by DoD (Award Number: W81XWH-20-2-0035).

Pediatric Pain

Comparative Analysis Of Immune Profiles In Youth With And Without High Impact Chronic Pain

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High-impact chronic pain(HICP) describes significant life interference due to chronic pain. While studies estimate the prevalence of HICP in youth to be between 5-10%, there is a need to further understand this condition and the underlying mechanisms. Several chronic pain conditions are associated with immunological and inflammatory processes (Wallace, 2015), suggesting a role of the immune response in HICP in youth. This preliminary study employed single-cell mass cytometry(MC) to compare immune profiles in youth with MSK pain, with and without HICP. The cohort included youth with MSK pain aged 11-18 enrolled in the SPRINT biomarker discovery study(n=142; NCT04285112). 53(37%) participants had HICP. For each participant, 1521 immune features were assessed in whole blood samples using a high-parameter MC immunoassay. Features included intracellular activities of signaling proteins measured across 49 innate and adaptive immune cell subsets at baseline(unstimulated) and Lipopolysaccharide(LPS) and Interleukin-2,4,6 -stimulated. Mann-Whitney U tests assessed group differences. Sixty features demonstrated significant between-group differences($p<0.05$, uncorrected). Markers related to immune activation(e.g., CD4+ T-cells, pMAPKAPK2, Ki67), inflammation(e.g., pNF-κB, pERK1-2, pSTAT5), and regulation(e.g., FoxP3+; memory; naïve Tregs) were observed. Median fold changes indicated both upregulation and downregulation of these features in the HICP group, suggesting that altered immune responses in youth with HICP

may contribute to adverse clinical outcomes. Future directions include multivariable modeling of high-dimensional MC data and data-driven selection of stratifying immune features using sparse machine learning. Elucidating the mechanisms underlying HICP may enhance our understanding of pain pathophysiology and inform early interventions to mitigate the long-term impact of chronic pain.

Maximizing Virtual Reality's Impact On Pediatric Pain: Insights From Usage Metrics
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Virtual Reality (VR) is a promising intervention for pediatric pain management as a stand-alone treatment and as a tool to enhance engagement in evidence-based strategies including physiotherapy (PT). Critical to its efficacy is sustained engagement yet research on supporting VR software is limited. We evaluated VR game usage patterns among youth with chronic pain in outpatient PT. Youth in a VR clinical trial received Oculus headsets to support engagement in PT. For each participant, app launches and duration were aggregated. Descriptive statistics were calculated to examine usage across games. Time series plots of daily play for participants were constructed, and visual analysis of trajectories conducted. Participants (N=34) averaged 2.3 VR sessions per week (0-9.3), each lasting ~11 minutes (0-29) and involving ~3.9 app launches (0-7.75). Overall, gameplay declined over time. Games with the most sustained engagement included FitXR, Beat Saber, and Fruit Ninja, accounting for 55% of the total 2141 launches and highest rates of revisits. By contrast, Nature Trek, Star Chart, and Wander constituted ~1% of total launches, with generally no revisits. A strong correlation exists between number of app launches and duration of app play (r=0.78); however, some games demonstrated good in-game retention (Golf+) but were less revisited, illuminating another important usage metric. VR use was variable and sustained engagement limited, highlighting the need to optimize games for youth with chronic pain. Games with high, sustained engagement involved more physical activity and featured competitive scoring. Future research should focus on identifying specific gameplay features contributing to sustained engagement in this population.

A Qualitative Analysis of Pain and Cognitive Impairment in JFM
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Juvenile-onset fibromyalgia (JFM) is a complex and disabling chronic musculoskeletal pain condition characterized by amplified widespread pain with features of disrupted sleep, fatigue, and cognitive dysfunction. The nature and severity of the relationship between pain and cognitive impairment experienced by youth with JFM is unknown and current measures of cognitive functioning do not capture the specific contexts in which difficulties emerge. The present study aimed to augment an existing youth self-report measure of cognitive symptoms (Behavior Rating Inventory of Executive Function, Second Edition; BRIEF-2) to maximize its content validity and clinical utility in JFM populations. Adolescents (ages 11-18) with JFM (n = 25) participated in semi-structured interviews. Interviews explored daily symptom manifestation (section 1). Then, a cognitive interviewing approach assessed participants' thoughts about

BRIEF-2 content by inquiring about existing item clarity, suggestions for additional items, and the interplay between cognitive and other JFM symptoms. Thematic analyses in section one revealed three core domains: functional disability, socio-emotional functioning, and interaction of pain. Cognitive interviewing indicated acceptable BRIEF-2 item clarity and minimal suggestions for modified content. However, participants described important differences in their experience of cognitive difficulties based on 1) environment (e.g., home versus school) and 2) JFM symptom status (e.g., fatigue and/or pain levels). This study improves our understanding of JFM through experiential descriptions linking pain, fatigue and cognitive difficulties. We aim to use findings to enhance the contextual relevance of current cognitive symptom measures, such as the BRIEF-2, and interventions that mitigate the disruptive effects of cognitive dysfunction in JFM.

Latent Analysis of Sleep, Pain, Affect, Cognition, and Energy Profiles Before Menarche Identifies Two Classes

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Following puberty, youth assigned female at birth (AFAB) experience higher rates of pain conditions, but little is known about predisposing factors. Conversely, the presence of the symptom cluster SPACE (Sleep disturbance, Pain of a widespread distribution, Affective perturbation, Cognitive disturbance, and Energy deficit) can identify adult chronic pain risk (Schrepf et al., 2018). This study applied latent class analysis (LCA) to identify subgroups within the SPACE framework in a community sample of 295 premenarchal AFAB youth (M age = 11.21 years, SD = 0.90, 88% White). Data was collected via surveys administered at baseline visit as part of a larger, longitudinal study examining dysmenorrhea. The following measures were utilized in the LCA: the PROMIS Parent Proxy Sleep Disturbance, Pain Body Maps, PROMIS Self-Report Positive Affect, BRIEF-2 (Behavior Rating Inventory of Executive Function) Parent, and the energy item from the Child Somatic Symptom Inventory. Based on model fit criteria (lowest BIC and LMR likelihood ratio test, $p < 0.001$) and parsimony, a two-class solution was selected. Class 1 (54% of the sample), termed “SPACE Sub-Clinical,” was characterized by mild sleep disturbance, greater widespread pain, lower positive affect, typical cognitive function, and low energy levels. Class 2 (46%), identified as “SPACE Normative Range,” exhibited normative sleep, no widespread pain, average positive affect, normal cognition, and normative energy levels. These findings suggest two distinct SPACE classes are identifiable in a community sample prior to menarche, and future research should examine if these latent classes differentiate pain trajectories and outcomes across the pubertal transition.

Adapting Pediatric Pain Programs for the Treatment of Functional Neurological Disorder - Theory and Outcomes

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Children and adolescents with chronic pain often present with comorbid conditions. Functional neurological disorder (FND) often co-occurs with chronic pain and has become an increasingly

common presentation in pediatric pain care. While the mechanisms involved in the development of chronic pain and FND are individually varied, complex, and multifactorial, the high rate of comorbidity may be attributed to the shared mechanism of autonomic dysfunction, resulting in a sustained activation of the autonomic nervous system despite the resolution/absence of objective threat/disease/damage. Given this overlap, intensive interdisciplinary pain treatment (IIPT) programs are uniquely suited to treat these patients using a biopsychosocial framework focused on functional restoration. Grounded in cognitive-behavioral treatment of pain, eating disorders, and anxiety, our team has developed a novel approach for treating youth with chronic pain and FND. Key components of intervention include externalization of pain/FND and use of individualized behavioral plans to target sense of control and selective attention to symptoms. A framework for implementing these novel strategies and individualizing them to diverse symptom presentations is outlined. Results from 41concurrently admitted patients (78% female, M age=14.84) who have completed this intervention are presented. Results indicate that patients demonstrated statistically significant decreases in Functional Disability Index scores from admission to discharge and maintained this improvement at 1- and 6-month follow-up. Additionally, they were able to independently manage symptoms once returning home suggesting that the proposed treatment is highly effective in improving function and coping. Dissemination will provide models of this adapted treatment to serve this increased clinical need.

Country-Level Contextual Factors and Adolescent Chronic Pain Across 44 Countries
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Adolescent chronic pain is highly prevalent, rising, and disproportionately impacts girls, yet macro-level country drivers remain poorly understood despite their role in shaping pain burden and disparities. Using data from the 2018 Health Behavior in School-Aged Children survey (N=244,097, ages 11-15), we examined the influence of critical country-level factors (GDP per capita, Human Development Index [HDI], child poverty rate, GINI Index, health expenditure, antenatal care coverage, traditional values, and self-expression values) on adolescent chronic pain and sex disparities across 44 middle- and high-income countries. Chronic pain, defined as at least weekly pain (headache, stomachache, backache, or multisite pain) over six months, ranged from 32.3% to 58.7% (overall 44.3%, I2=99.1%). Multilevel logistic regressions, controlling for individual-level covariates, revealed limited associations between contextual factors and chronic pain across the overall sample. However, sex-specific effects emerged. Among adolescent females, higher HDI (an economic composite measure encompassing health, education, and standard of living) was associated with higher odds of any chronic pain (OR=1.11, 95% CI 1.02-1.21), chronic stomachache (OR=1.15, 95% CI 1.03-1.28), and chronic multisite pain (OR=1.14, 95% CI 1.03-1.26), while greater self-expression values (a socio-cultural measure emphasizing autonomy and quality of life) was associated with higher odds of chronic stomachache (OR=1.15, 95% CI 1.03-1.29). High global adolescent pain burden warrants focused attention. Future studies should include data from lower-income countries to better understand macro-level determinants of global adolescent pain burden.

Retrospective Categorization Of ICD-10 to ICD-11 Diagnostic Codes Among Treatment-

Seeking Youth with Chronic Pain: Implications For Research and Treatment
Robert Gibler, Christopher King, Andrew Collins, Kenneth Goldschneider, Cheryl Hartzell, Alexandra Szabova, Susmita Kashikar-Zuck, Anne Lynch-Jordan; University of Kansas Medical Center

The ICD-11 introduced changes in pain classification consistent with the biopsychosocial model. Its applicability to pediatric pain is not well understood, underscoring the need to assess its diagnostic utility and relationships with psychosocial and functional outcomes. We retrospectively applied ICD-11 criteria to reclassify youth with ICD-10 pain diagnoses and examined whether psychosocial factors and functional disability differentiated ICD-11 diagnostic groups.Participants (AgeM=15.0, 80.4% female) presented for evaluation in a multidisciplinary pain clinic at a large children's hospital between 2017-2019 and completed psychosocial measures (e.g., FDI, PROMIS-Anxiety and Depressive Symptoms). Participants' ICD-10 diagnoses listed in the medical record were re-classified based on ICD-11.The most common ICD-10 pain diagnoses were widespread musculoskeletal and/or joint(s) (41%), back (18%), abdominal/flank (15%), and leg/lower extremity pain (12%). ICD-11 reclassification revealed secondary musculoskeletal pain (45.3%), primary musculoskeletal pain (22.4%), primary widespread pain (8.4%), and primary visceral pain (7.8%) as the predominant categories. ICD-11 reclassification decreased widespread pain classification (41% to 8.4%). The most common diagnoses resulting in a "shift" from an ICD-10 widespread musculoskeletal/joint pain diagnosis to an ICD-11 secondary diagnosis were connective tissue disorders (e.g., Ehlers-Danlos syndrome, joint hypermobility). Pain, anxiety, and depressive symptoms did not vary significantly across groups, but the chronic primary widespread pain group reported the highest FDI scores (M=31.13, SD=2.84).Diagnostic reclassification using ICD-11 was feasible but revealed challenges in distinguishing primary versus secondary pain, especially for youth with co-occurring conditions (e.g., EDS). Research into the biology of chronic pain is needed to refine ICD-11's clinical utility and inform treatment.

The Development and Validation of the Pain-related Stigma Scale for Adolescents (PReSS-A) with Chronic Pain
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Adolescents with chronic pain may experience stigma related to their condition, but the lack of validated measures for assessing pain-related stigma limits our understanding of its prevalence and impact. The present study describes the development and validation of the self-report Pain-related Stigma Scale for Adolescents (PReSS-A) and the assessment of stigma across multiple relational contexts. The sample consisted of 286 adolescents (aged 12-17) with juvenile fibromyalgia (JFM; n = 129), other chronic primary musculoskeletal pain conditions (CPMP; n = 32), juvenile idiopathic arthritis (JIA; n = 32), and Disorders of Gut-Brain Interactions (DGBI; n = 93) across four pediatric hospitals. An exploratory factor analysis (EFA) was conducted to examine the instrument's underlying structure. Stigma dimension scores were compared across adolescents with different chronic pain conditions. Our findings indicated that the PReSS-A total score and each subscale score (felt stigma, peer stigmatization, internalized stigma, and

anticipatory stigma/concealment) demonstrated strong internal consistency. Construct validity was supported by correlations between subscale and total scores and related constructs. The EFA identified two factors for the PReSS-A: felt stigma and internalized stigma. Adolescents with JFM reported greater pain-related stigma than those with other conditions ($F(3, 278) = 19.36$, $p < .001$). The PReSS-A is the first pain-related stigma measure validated across different chronic pain conditions and can advance research on pain-related stigma among adolescents. Future studies should prioritize examining the impact of pain-related stigma on functioning and social development in this population. This research is supported by the National Institute Of Arthritis And Musculoskeletal And Skin Disease of the National Institutes of Health under Award Number K23AR073934 and in collaboration with the Multi-site clinical trial of Fibromyalgia Integrative Training for Juvenile Fibromyalgia (FIT Teens; NIAMS Grant # R01-AR070474PI: Kashikar-Zuck, Cincinnati Children's Hospital). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Unmet Psychosocial Needs In Pain Care For Pediatric Rheumatic Diseases: A Qualitative Inquiry

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Pediatric rheumatic diseases (PRDs) are a group of inflammatory and autoimmune conditions such as juvenile idiopathic arthritis, systemic lupus erythematosus, and juvenile dermatomyositis. Despite great advancements in treatment for PRDs, approximately one third of youth with PRDs report chronic pain and fatigue and often experience reduced quality of life relative to healthy peers. Thus, we are conducting a qualitative study as a part of a larger intervention study to understand the current treatment gaps and psychosocial needs of patients with PRDs living with ongoing pain and fatigue. Qualitative data collection is ongoing and will continue until data saturation is reached. Twelve stakeholders including 10 healthcare providers (physicians, psychologists, physical and occupational therapists) and 2 adult caregivers of youth with PRDs have been interviewed to date. Interviews were independently coded by two members of the research team and discrepancies were resolved following the coding of each interview. Thematic analysis of codes was conducted (Braun and Clarke, 2006). Initial results revealed that healthcare providers and caregivers identify unmet psychosocial needs in treatment including a lack of integrated psychological support in clinic settings for pain concerns and challenges with medication adherence. Caregivers also emphasized that patients (and the caregivers themselves) would benefit greatly from peer/family interaction with other individuals who are facing similar concerns. Thus, we anticipate that group settings may be positive treatment outlets. Further, integrated psychological support in rheumatology clinics and opportunities for patient and caregiver socialization could improve quality of interdisciplinary care for youth with PRDs.

Systematic Review and Meta-Analysis of Psychological Intervention on Anxiety, Functioning, and HRQOL in Pediatric Chronic Pain Patients

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Youth with chronic pain often experience anxiety; however, the effectiveness of psychological interventions in reducing anxiety in chronic pain populations is unknown. Utilizing systematic review and meta-analysis, we aimed to assess effectiveness of psychological interventions for youth with chronic pain seeking anxiety treatment. A subset of data from a larger systematic review and meta-analysis were utilized. Results of this larger systematic review demonstrated significant reductions in anxiety following psychological treatment in youth with chronic medical conditions. Current analyses utilized randomized controlled trials (RCT) of pediatric (≤24 years) chronic pain patients receiving psychological interventions. Impact of intervention on anxiety, functional impairment, and health related quality of life (HRQOL) were assessed. Manuscripts from Medline, Embase, PsycInfo, and CENTRAL databases were screened using Covidence software. Meta-analysis was completed using R. Study quality was assessed via Cochrane Risk of Bias version 2. Meta-analysis included 15 RCTs (N = 1924 participants). Risk of bias was low in 60% of studies (n = 9). Psychological interventions did not significantly impact anxiety (Hedges' g = -0.1208 [-0.3368; 0.0953]), functional impairment (Hedges' g = 0.3604 [-0.5914; 1.3121]), or HRQOL (Hedges' g = 0.2481 [-0.4137; 0.9099]). Neither intervention modality nor anxiety as the treatment target impacted results. Contrasting results of psychological intervention in youth with a variety of chronic medical conditions, present findings suggest current psychotherapies do not significantly address anxiety for youth with chronic pain. Functioning and HRQOL were also not significantly addressed by these interventions. Research must critically assess the unique psychotherapeutic needs of pediatric pain patients.

Musculoskeletal Pain Is Not All The Same: Evoked Quantitative And Brain Sensory Processing In Youth With And Without Comorbid Hypermobility

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Hypermobility disorders (HD) affect approximately 1 in 600 to 1 in 900 individuals globally and have significant physical and psychological implications. Compared to healthy peers, patients with HD exhibit lower pressure-pain thresholds (PPT) and higher temporal summation of pain (TSP). The mechanisms underlying these changes and their specificity to HD versus general musculoskeletal (MSK) pain remain unknown. This study employs quantitative sensory testing (QST) and multisensory task-evoked fMRI to compare sensory processing in youth with MSK pain, with and without comorbid HD. This sample included youth with MSK pain aged 11-18 enrolled in a biomarker discovery study (n=193; NCT4285112). Within this cohort, 62 (32%) had HD, with 118 randomly selected age- and sex-matched youth without HD. QST metrics included MDT, MPT, MPS, PPT, TSP, and CPM. fMRI metrics included multisensory task-based evoked response and ROI connectivity (RRC). Two-sample T-tests assessed group differences. Youth with comorbid HD reported significantly higher MDT and PPT in several muscle groups and lower pain intensity/unpleasantness during TSP tasks ($p<0.05$). fMRI analysis revealed greater activation in the superior/medial/inferior frontal gyri and cingulate gyrus among youth with comorbid HD, as well as higher RRC between the rACC-NAC, vmPFC-PostCC, and thalamus-rACC ($p<0.05$). Youth with MSK pain and comorbid HD may exhibit an anti-nociceptive and hypoesthetic profile. Lower TSP may reflect enhanced endogenous pain

modulation aided by engagement of cognitive strategies mediated by strong RRCs (e.g., vmPFC-PostCC) resulting in dampened pain perception and highlighting an interplay between cognitive and emotional pathways in pain processing.

Increased Testosterone Predicts Decreased Pain Inhibition Over Time: An Exploratory, Longitudinal Study in Healthy Adolescent Girls

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Adolescence is a period of significant physical change marked by drastic changes in sex hormone levels that can impact the trajectory of health into adulthood. In healthy adolescents, experimental pain sensitivity typically decreases throughout this period, but the factors contributing to this change are poorly understood. The aim of this exploratory analysis was to examine changes in and the relationship between sex hormone levels and pain sensitivity over time. Healthy girls (n=29, 9-16 years) completed a battery of quantitative sensory testing (QST) to assess pain thresholds, tolerance, and modulation to pressure and thermal pain at baseline and a 1-year follow-up. Blood samples were analyzed for sex hormone levels. QST measures that significantly differed from baseline to follow-up were used as dependent variables in bootstrapped multiple regression models. The change in sex hormones served as separate predictors. Covariates included age at baseline and change in pubertal status using the Pubertal Development Scale. Pressure conditioned pain modulation (P-CPM) significantly decreased over time (Δ=-59.47 kPa, p=.021), indicating worsening pain inhibitory capabilities. Conversely, cold pain tolerance significantly increased over time (Δ=20.59 sec, p=.008). No regression models significantly predicted the change in cold pain tolerance. Models including the change in androgens (total-, bioavailable-, and dihydro-testosterone) showed a significant negative relationship with P-CPM ($\Delta R2$ range=0.500 to 0.536; β range=-0.747 to -0.817; p<.001). This suggests that contrary to its antinociceptive property found in adults, increased testosterone in healthy adolescent girls over time is associated with worsening pain inhibitory capabilities beyond the influence of age and pubertal status.

Investigating Pain and Associated Cognitive Symptoms in Adolescent Cancer Survivors of Acute Lymphoblastic Leukemia

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Long-term survivors of pediatric cancer are at increased risk of experiencing pain, yet little is known about mechanisms underlying pain or its association with functional outcomes. This study explored associations between pain symptoms with cognition and serum biomarkers of inflammation, oxidative stress, metabolic and cardiovascular function, and bone remodeling to inform potential underlying mechanisms. Participants included adolescent survivors of ALL treated on a chemotherapy only protocol (N=113), who were between 5- and 10-years post-diagnosis (M[SD] Age = 14.36[4.56], 56.25% female). Pain intensity, joint pain, and cognitive problems were parent-reported using the Pediatric Quality of Life Inventory - Cancer Module

(PedsQL-C) during a visit to the After Completion of Therapy Clinic, and biomarkers were assessed through serum collected on the same visit. Linear regression models examined associations between pain, cognition, and biomarkers, adjusting for age, sex, and time since diagnosis. Pain and cognitive problems were respectively reported for 30% and 57% of survivors. Greater joint pain was associated with more severe cognitive problems (β=-5.43, p=0.04). Higher pain intensity correlated with lower levels of malondialdehyde (MDA) (β=-0.17, p=0.04), carboxy-terminal crosslinked telopeptide of type 1 collagen (CTX-1) (β=-918.65, p=0.03), and dehydroepiandrosterone sulfate (DHEAs) (β=-25.48, p=0.04), while greater joint pain correlated with higher CTX1 (β=855.78, p=0.03) and DHEAs (β=20.63, p=0.06). Overall, pain was associated with cognitive disruptions and biomarker alterations, suggesting potential links between neurocognitive burden and peripheral pain modulation or bone resorption. Future work should explore causal pathways between pain, cognition, and biomarkers to develop targeted interventions for pain management in this population.

Exploring Hippocampal Volumes And Cognitive and Psychological Function in Youth with Chronic Widespread Pain

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Chronic widespread pain (CWP) in youth is associated with significant disability and psychological impairment. The hippocampus, critical for memory, emotions, and learning, may influence the development and progression of chronic pain. Decreases in hippocampal volumes have been observed in chronic pain patients, but its role in adolescent cognitive function remains understudied. This study explores the relationship between psychological and pain-related characteristics with hippocampal volumes in CWP patients, to provide insight into the impact of CWP and identify targets for pediatric pain treatment. This study applied neuroimaging and pain measures to understand CWP in pediatric patients (ages 11-17) with CWP. Participants completed questionnaires on depressive symptoms, anxiety, and pain-related function. MRI scans were processed through Freesurfer V.7.4 with a focus on hippocampal volumes. Statistical analysis for pain measures and volumetric differences were analyzed using SPSS V.29. Significant positive correlations were seen between difficulties in concentration and memory and levels of functional disability ($p = 0.004$), anxiety ($p = 0.013$), depressive symptoms ($p = 0.006$), stress ($p = 0.002$), and pain catastrophizing ($p = 0.006$). Smaller hippocampal volumes showed a trend towards correlation with increased difficulties in concentration and memory. Findings suggest cognitive difficulties in chronic pain are influenced by psychological/physical factors, impacting daily functioning. The observed trend towards correlation between hippocampal volume and difficulties in concentration and memory indicates a potential link between hippocampal structural changes and greater cognitive impairment. Larger studies could clarify this relationship and explore hippocampal changes and chronic pain in youth.

Safety and Outcomes of Intensive Interdisciplinary Pain Treatment for Pediatric Patients with Generalized Joint Hypermobility

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One common yet understudied comorbidity in pediatric chronic pain is generalized-joint-hypermobility (GJH). Intensive interdisciplinary pain treatment (IIPT) is an effective treatment option for pediatric patients with high-impact pain; however, the safety and effectiveness of IIPT for patients with comorbid GJH has not been examined. This study assessed prevalence of injuries and physical and psychological outcomes of IIPT for pediatric patients with chronic pain with and without GJH. A retrospective review of 306 patients admitted to an IIPT program in the midwestern United States (mean age=15.3(2.1), 84% female) identified 14.7% who were medically diagnosed with GJH. IIPT included 40 hours per week of physical and psychological therapies for 4-6 weeks. Joint protective methods were utilized for patients with GJH. During treatment, all participants had daily medical evaluation which included assessment of injuries. Pain, pain-catastrophizing, physical impairment, anxiety, depression, and quality of life were measured via standardized self- and parent-report measures at baseline, weekly during treatment, and 1-month, 6-month, and 1-year follow-ups. There was no association between GJH and injury during IIPT, $X2(3)=4.09$, $p=0.25$. Patients with and without GJH demonstrated significant improvements on all outcomes that were maintained at all follow-ups (all $ps<.01$). Hierarchical linear modeling indicated no significant differences by GJH; however, improvements in internalizing symptoms may not be as well-maintained in patients with GJH, including anxiety, depression, and parent-reported emotional functioning. Overall, these findings suggest IIPT is safe and effective for pediatric patients with GJH, yet further research is needed to clarify the unique psychological needs of patients with GJH.

Bridging the Gap: Advancing Chronic Pain Solutions for Autistic Youth Through Collaborative Training and Innovation

Rocco Iacobone, Jacqueline Warner, Allison Hatley-Cotter, Janette Long; Nationwide Children's Hospital

Individuals with autism spectrum disorder (ASD) have comorbidities and characteristics that predispose them to pain, with research demonstrating higher prevalence of pain symptoms and pain-related functional impairment among autistic youth (Mazurek et al., 2014; Whitney & Shapiro, 2019). Currently, there is limited research examining chronic pain treatments with autistic youth who may present with unique needs compared to neurotypical populations (Han et al., 2024). The purpose of this study is to describe a professional collaboration between the Center for Autism Spectrum Disorder and Pediatric Pain Psychology providers at Nationwide Children’s Hospital, which aimed to address this intersectionality specifically for implementation of the Comfort Ability® Program (CAP), an evidence-based chronic pain program. This quality improvement project used the Plan-Do-Study-Act cycle. A preliminary needs assessment gathered qualitative feedback from Applied Behavior Analysis (ABA) practitioners and identified training gaps pertinent to treating youth with ASD and chronic pain. Subsequent cross-training sessions in chronic pain interventions were provided to four ABA practitioners, who then served as co-facilitators for implementation of CAP. Outcomes included increased provider comfort, enhanced awareness of this population’s unique needs, and an institutional partnership to ensure sustainability. There exists a distinct population of individuals who are dually diagnosed with ASD and chronic pain discomfort. It is feasible to cross-train staff in both ASD

treatment and chronic pain management modalities, enhancing the effectiveness of interventions by integrating knowledge and skills from both areas to manage unique needs more effectively.

Characterizing Temporomandibular Disorder Pain in Adolescents

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Pain associated with temporomandibular disorders (TMD) is the leading non-odontogenic cause of orofacial pain among youth. The objective of this study was to characterize the phenotype of TMD pain in adolescents. The validated three screening questions for TMD was used to identify adolescents (10-19 years) with TMD pain. Participants completed the Revised Child Anxiety and Depression Scale, Perceived Stress Scale for Children, modified Symptom Questionnaire developmentally relevant for adolescents, and Graded Chronic Pain Scale. Pearson's correlation was used to investigate significant relationships between pain intensity and pain-related interference with psychological distress measures. Psychological and pain outcomes were compared among participants based on presence of specific symptoms (e.g., temporomandibular joint (TMJ) sounds, jaw locking, headache) with independent t-tests and ANOVA (Tukey as post hoc tests). 34 adolescents (15.1±2.3 y/o, 61.8% females) were included in this prospective study. Stress, anxiety, and depression measures were all positively correlated among each other (all p's <.001). Greater pain intensity was significantly correlated with pain-related interference ($r(34)=.608$, $p<.001$), but not with psychological distress symptoms (all p's>0.05). TMJ sounds and intermittent locking were reported by 76.5% and 38.2% of participants, respectively. Those who suffered from headache at least one day per week (reported by 45.5% of participants) had significantly higher pain interference ($p=.007$) and pain intensity ($p=.003$) than those without headache. Understanding the phenotype of TMD pain during adolescence is crucial for identifying potential risk factors for the persistence of TMD pain into adulthood.

Reduction in Fear of Movement Predicts Long-Term Decreases In Functional Disability Among Adolescents With Juvenile Fibromyalgia

Nuria Morales Coskran, Cecelia Nelson, Megan Pfeiffer, James Peugh, Kimberly Barnett, Mark Connelly, Kim Klages, Deidre Logan, Anne Lynch-Jordan, Sarah Nelson, Emily Wakefield, Sara Williams, Susmita Kashikar-Zuck; Cincinnati Children's Hospital Medical Center

Pain catastrophizing and fear of movement are common in adolescents with juvenile fibromyalgia (JFM) and have been shown to be associated with higher levels of pain intensity and functional disability. This study tested the hypothesis that improvements in pain catastrophizing and fear of movement would predict long-term changes in functional disability following a non-pharmacologic (behavioral and exercise) intervention. Adolescents with JFM (N=317, Mage=15.76, 86.4% female, 84.2% White) received either cognitive-behavioral therapy (CBT), graded aerobic exercise, or a combined CBT and neuromuscular exercise training program (Fibromyalgia Integrative Training; FIT Teens) as part of their participation in a multi-site randomized controlled trial. The primary finding of the trial was that functional disability significantly improved at 3-month follow-up across all three treatment conditions. To analyze whether pre/post-intervention changes in pain catastrophizing and fear of movement predicted

functional disability outcomes at 3- and 12-months follow-up, we employed a novel latent curve modeling using an incremental validity framework for estimating distal outcomes across all three treatment groups. Results indicated that post-treatment improvements in pain catastrophizing and fear of movement both significantly predicted reductions in functional disability at the 3-month follow-up (p's<.05). However, only a reduction in fear of movement predicted a reduction in functional disability at the 12-month follow-up. Results support targeting pain catastrophizing and fear of movement in non-pharmacologic interventions for JFM. Reducing fear of movement appears to be particularly important, as it was associated with sustained improvement in disability over the 12-month post-treatment period. Funding: NIH/NIAMS Grant #s R01 AR070474 and P30 AR076316.

Pain Experiences Among Children Receiving Treatment for Acute Lymphoblastic Leukemia

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Over 3,000 children are diagnosed with acute lymphoblastic leukemia (ALL) each year in the United States, making ALL the most prevalent childhood cancer. Pain is prevalent in ALL, often resulting from disease processes, chemotherapy treatment, and invasive medical procedures. However, the full complexity and nature of the pain experience in children undergoing ALL treatment remains understudied. This study aimed to qualitatively examine pain experiences in children with ALL over the course of treatment. Children (ages 8-17) and caregivers of children with ALL (child ages 2-17) participated in 6 semi-structured interviews during critical phases of ALL treatment: induction, consolidation, interim maintenance, delayed intensification, and maintenance. Interviews were audio recorded and transcribed. Data is being analyzed via thematic analysis using NVivo (Version 20). Twenty-one caregivers and 8 patients participated (Mage=9.6 [SD=5.7]; 56% female; 100% White; 6% Hispanic/Latino). Data analysis is ongoing, with emerging themes expected to identify common types of pain (i.e., acute, neuropathic, chronic), sources of pain (i.e., medical procedures, chemotherapy agents), and pain coping strategies over the ALL-treatment course. This study will enrich our understanding of pain in pediatric ALL. Pain assessment in pediatric cancer is complex due to the varying clinical manifestations and contributory factors over the course of treatment. Research is needed to further examine pain in pediatric ALL, as well as to identify predictors of risk for development of chronic pain, to inform more effective pain management approaches for this population.

Prevalence And Impact Of Adverse Childhood Experiences Among TEACH (Treatment And Education Approach For Childhood-onset Lupus) Participants

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Exposure to adverse childhood experiences (ACEs) is associated with negative physical and mental health outcomes for youth with childhood-onset systemic lupus erythematous (cSLE), an autoimmune condition characterized by pain, fatigue, and mood problems. Although cognitive behavioral interventions may be beneficial, it is unknown whether ACEs impact response. This

study examined the prevalence and impact of ACEs on youth participating in a multi-site randomized control trial of the Treatment and Education Approach for Childhood-onset Lupus (TEACH; a cognitive-behavioral program to manage pain, fatigue, and mood symptoms) from 2020-2023. Youth's ACE exposures, average pain intensity, fatigue, depressive, and anxiety symptoms were reported at baseline and eight weeks after completing TEACH. Analyses of covariance modeling with interaction terms examined whether TEACH-effects varied by ACE exposure for pain, fatigue, depressive and anxiety symptoms separately. Data were reported by 64 youth with cSLE (ages 12-20 years; mean 16.6), 32 of whom received TEACH. Nearly half (n=26; 46.4%) reported ≥1 ACE, with 16.1% reporting 3-4 exposures. TEACH participation was associated with improvements in fatigue (adj. β -4.12 (95% Confidence Interval [CI] (-7.71,-0.53)), depressive (adj. β -7.84 [-12.46, -3.22]), and anxiety symptoms (adj. β -0.36 [-0.70, -0.01]), which did not vary by ACE exposure. ACEs did not independently affect pain, fatigue, or mood symptoms. Our findings suggest that while ACEs are prevalent among youth with cSLE, psychological treatment may be comparably efficacious for fatigue, depression, and anxiety symptoms regardless of exposure. Funded by the Lupus and Allied Diseases Association, Childhood Arthritis and Rheumatology Research Alliance—Arthritis Foundation.

Bullying and Pediatric Chronic Pain: Racial/Ethnic Disparities among Asian and White Youth

Yoonhee Kim, Ryan Ma, Jennifer Rabbitts, Cornelius Groenewald; Stanford University School of Medicine

While bullying victimization has been linked to pediatric chronic pain, the impact of victimization and perpetration across racial/ethnic groups remains understudied. Asian American youth report the highest level of discrimination, but consistently low rates of chronic pain, presenting an underexamined dynamic. We aim to examine associations between chronic pain and bullying victimization and perpetration, with a focus on comparing Asian and White youth in the US. We conducted a cross-sectional analysis of the 2018-2022 National Survey of Children's Health (NSCH), including children 2-17 years old (n=118,634). Chronic pain was defined as caregiver-reported frequent or chronic physical pain in the past 12 months. Caregivers reported bullying victimization and perpetration incidents within the same period. Children with chronic pain experienced higher rates of bullying victimization (17.7%) compared to the national average (11.79%)(Pearson chi2: $p<0.0001$). Associations between bullying victimization and chronic pain remained significant in multivariate Poisson regression (adjusted prevalence ratio (aPR)=2.14, 95% Confidence Interval (CI): 1.96-2.33, $p<0.0001$). Similarly, bullying perpetration was more common among children with chronic pain (6.87%) than those without (3.2%)($p<0.0001$) and the association remained significant in multivariate analyses (aPR=1.65, 95%CI: 1.41-19.3, $p<0.0001$). Asians reported lowest rates of bullying victimization (4.4% versus 13.69% for Whites) and perpetration (1% vs. 3.98% for Whites). Thus, youth with chronic pain are more likely to be victims and perpetrators of bullying, highlighting the social impact of chronic pain and its relevance to clinical assessment and intervention. Differences between Asian and White youth in bullying and its association with chronic pain warrant further investigation.

Pain And Pain Interference in Children and Adolescents Seeking Weight Management

Intervention: An Analysis of Data From a Multisite Observational Study
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Research indicates that pain and obesity frequently co-occur, and this comorbidity may diminish the effectiveness of multidisciplinary pediatric pain management interventions. However, pain and its impact have not been well characterized in youth with obesity. We analyzed data from a multi-site longitudinal study examining predictors of attrition from pediatric weight management (SIT (Stay In Treatment) Study). We examined pediatric participants' scores on measures of pain intensity (PROMIS-Pain Intensity) and impact (PROMIS-Pediatric Pain Interference scale) at their first weight management appointment. We also investigated how pain and pain interference related to social-emotional and physical functioning (PROMIS-Anxiety, Depressive Symptoms, Fatigue, Peer Relationships, and Mobility). 433 youth completed their baseline visit (Mage = 11.92; 52.4% non-White, biracial, or multi-racial; 22.2% Hispanic; MBMI%ile = 98.82). One-third of youth reported moderate-to-severe pain intensity in the previous week. Average pain interference scores were in a normative range (M=47.96, SD=8.70). However, 26.1% and 7.4% reported moderate and severe pain interference, respectively, based on established cut-offs in pediatric pain samples. Pain intensity and interference were positively associated with anxiety, depressive symptoms, and fatigue (Pearson's r range = 0.40-0.49; p's<0.001), and negatively correlated with perceived peer relationship quality and mobility (r range = -0.19-0.34; p's<0.001). This study indicates that youth presenting for weight management treatment frequently experience pain, and a considerable proportion report significant pain-related interference with daily living. Psychosocial factors were strongly related to pain, suggesting that biopsychosocial conceptualizations of pain may inform tailored treatment efforts for this vulnerable population.

Pain Attitudes and Coping: Examining Relationships with Pain Severity and Interference
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Ehlers-Danlos Syndromes (EDS) is a family of heritable connective tissue disorders associated with joint hypermobility and chronic pain. The unique pain experiences of patients with EDS are not well-established. This study examined the relationships between participants' attitudes about their pain, the coping strategies they employ, and self-reports of pain severity and interference. One-hundred and twenty-eight patients with EDS (73% female; 87% White, 8% multiracial) completed the Brief Pain Survey, the Pain Coping Questionnaire, and the Pain Stages of Change Questionnaire as part of clinical care. Emotion-focused avoidance strategies were positively correlated with the pre-contemplation (r=0.612, p<.001) and contemplation stages (r=0.343, p<.001) and negatively correlated with the maintenance stage (r=-0.310, p<.001). Problem-focused avoidance strategies were negatively correlated with the pre-contemplation stage (r=-0.354, p<.001) and positively correlated with the action (r=0.262, p=.003) and maintenance stages (r=0.369, p<.001). Approach-focused coping strategies were positively correlated with the contemplation (r=0.246, p=.005), action (r=0.473, p<.001), and maintenance (r=0.430, p<.001) stages. Pain severity was positively correlated with emotion-focused avoidance strategies (r=0.332, p<.001) and the pre-contemplation (r=0.355, p<.001) and contemplation (r=0.213,

p=.016) stages. Pain interference was negatively correlated with problem-focused avoidance strategies (r=-0.260, p=.003) and positively correlated with the pre-contemplation (r=0.471, p<.001) and contemplation (r=0.265, p=.003) stages. This study demonstrates that, as participants progress along the stages of change, they are more likely to employ primary and secondary coping strategies and less likely to employ passive coping strategies, and that higher pain severity and interference are associated with lower readiness to adopt a self-management approach to chronic pain.

Overweight, But Not Obesity, Impedes Psychosocial Improvement in Youth with Chronic Pain

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Obesity impedes functional improvement in youth with chronic pain. Given the interplay between socioemotional concerns, and both chronic pain and obesity in children, the aim of this study was to examine whether in youth with chronic pain, obesity also impedes improvement in anxiety and depression. Participants included 700 patients presenting to a multidisciplinary pediatric chronic pain clinic for evaluation (8-18 years; 70% female; 88% White). PROMIS anxiety and depression measures were completed at three timepoints: pre- evaluation (=Baseline), and at ~one (=Follow-up 1) and ~three (=Follow-up 2) months after evaluation. Weight groups included underweight (U; BMI percentile < 5), healthy weight (HW; BMI percentile= 5-84.99), overweight (O; BMI Percentile= 85-94.99) and obese (Ob; BMI Percentile > 95). Change over time was assessed using a general linear mixed model. Key findings include: 1) Anxiety improved from baseline to both follow-up 1 and follow-up 2 in HW ($p<0.0001$ for both timepoints) and Ob ($p<0.001$ for both timepoints) groups., 2) Depression improved from baseline to follow-up 1 in both HW ($p=0.002$) and Ob ($p=0.024$) groups. In the Ob group, there was also a significant improvement from baseline to follow-up 2 ($p=0.003$)., and 3) for the O group, neither anxiety nor depression improved over time. Contrary to expectations, youth with Ob improved in anxiety and depression over time, whereas the youth with overweight stagnated. Among youth with chronic pain, those with overweight do not appear to benefit from multidisciplinary pain management and may need additional resources.

Role of Stress on Venipuncture Pain in Adolescents

Joel Brown, Zoe Ademuyiwa, Hadas Nahman-Averbuch; Washington University in St. Louis

Venipuncture is a painful and stress-inducing procedure, especially in the pediatric population. The effect of stress-related venipuncture on the coupled pain is still unclear. we aimed to examine the relationships between stress (venipuncture-related and general) on venipuncture pain, hypothesizing that higher stress levels would be related to higher pain levels. 40 adolescents (5 boys, mean age 12.13±1.32) participated in the study which, included completing questionnaires and a blood draw. General stress was collected using the Perceived Stress Scale. Immediately before the blood draw, participants were asked to rate their venipuncture-related stress level using Visual Analog Scale (VAS) (ranged from “no stress at all” to “the most stressed

imaginable"). Following venipuncture, participants rated their pain intensity and pain unpleasantness using VAS (ranged from "no pain intensity/no pain unpleasantness" to "most intense pain sensation imaginable/most unpleasant sensation imaginable"). Regression models were used to assess the relationships between pain and stress controlling for age and sex. Interestingly, only higher venipuncture-related stress was related to higher pain intensity (estimate (SD)= 0.192 (0.062), t ratio=3.08, r2=0.292, p=0.005) and pain unpleasantness (0.423 (0.173), t ratio=2.45, r2=0.207, p=0.022). However, no relationships were found with general stress and pain intensity (0.041 (0.039), t ratio=1.06, r2=0.043, p=0.301) and unpleasantness (0.099 (0.103), t ratio=0.97, r2=0.036, p=0.344). General stress may be different from specific venipuncture-related stress with the latter having greater influence on pain-related venipuncture. Developing interventions focusing on reducing stress-related venipuncture in adolescents rather than general stress could assist in reducing pain and increase willingness to undergo needle procedures.

The Relationships Between Pro-Inflammatory Cytokines and Depression in Adolescents with Chronic Pain

Emma Gaydos, Katrina Guardino, Emma Biggs, Sarah Nelson, Laura Simons; Stanford University School of Medicine

Introduction Depression and chronic pain have high comorbidity among adolescents and share proposed underlying mechanisms, including elevation of pro-inflammatory cytokines. This study examines differences in IL-1β, IL-6, IL-8, and TNF-α levels between adolescents with chronic pain and pain-free peers and their relationship to depressive symptoms and pain outcomes. Methods The study included 54 adolescents with chronic pain and 24 pain-free peers (ages 10-24). Participants completed surveys assessing depressive symptoms, perceived distress, and pain outcomes. Cytokines were assessed via saliva samples. T-tests compared cytokine levels between groups. Partial correlations assessed relationships between cytokines, depressive symptoms, and distress among the pain and pain-free groups and relationships between cytokines, depressive symptoms, and pain outcomes among the pain group. Results The chronic pain group (M=9.43,SD=11.26) showed elevated IL-6 levels compared to pain-free peers (M=7.09,SD=12.66), t(63)=2.48,p<.01. IL-1β and IL-6, respectively, were positively related to depressive symptoms (r=.162,p=.03;r=.226,p=.002) and perceived distress (r=.383,p<.001;r=.328,p=.002) among adolescents with chronic pain and pain-free peers. Among the pain group, IL-6 was positively associated with functional disability (r=.281,p<.01), pain severity (r=.235,p=.03), and perceived distress (r=.320,p<.01), but not pain catastrophizing, fear of pain, or depressive symptoms. In contrast, IL-1β was positively associated with pain catastrophizing (r=.238,p=.02), fear of pain (r=.220,p=.04), depressive symptoms (r=.223,p=.04), and perceived distress (r=.399,p<.001), but not pain severity or functional disability. TNF-α and IL-8 showed no significant associations. DiscussionFindings suggest that IL-6 and IL-1β are key players in chronic pain and depression. IL-6 is more associated with physical symptoms, while IL-1β relates more to psychological factors like fear-avoidance.

Describing Pediatric Intraoperative Methadone Outcomes Using the PHIS Dataset

Zoe Peach-Riley, Cornelius Groenewald; Stanford University School of Medicine

More than 4 million operations are performed on children in the United States each year. By some estimates up to 40% of children suffer from moderate to severe pain after surgery. Acute pain following surgery is associated with significant adverse effects, including delayed functional recovery and increased use of opioid medications. Patients administered methadone intraoperatively report less pain and use fewer opioids in the post-operative period. However, the safety of methadone administration to children during the intraoperative period has not been established. Using the Pediatric Health Information System (PHIS) database, we analyzed discharge data from teenagers (age 12-19) (n=25,713, mean age=16 years, male = 57%, female=43%) who had undergone outpatient orthopedic surgery. We hypothesized that post-surgical hospital readmissions would be more prevalent among children administered intraoperative methadone as compared to those who did not receive methadone because of opioid-related side effects. In our sample 82 children received methadone, while 25,631 did not. We found that 1.2% of patients administered methadone were readmitted to the emergency department (n=1) compared to 0.4% of patients who did not receive methadone (p=0.29). Statistical analyses thus do not confirm our hypothesis in this sample. Further research will aim to expand sample size, particularly the subset of patients administered intraoperative methadone. Additionally, we aim to examine specific readmission scenarios with greater specificity, especially in the context of post-surgical pain.

Validation Oof a Proxy- and Self-Administered Sensory Testing Tool-Kit in Youth
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Quantitative sensory testing (QST) is a set of methods for quantifying somatosensory functioning. Limitations of laboratory-based QST (LQST) include high cost, complex training, poor portability, and lengthy testing time. Translating QST to a home setting could facilitate future research and clinical care. The objective of this study was to evaluate a proxy/self-administered QST (P/SA-QST) tool-kit to detect changes in sensory and pain processing in youth. We recently reported on the validation of P/SA-QST in healthy young adults. The P/SA-QST tool-kit is safe, easy to use, and uses widely available tools corresponding to components of LQST. We are recruiting 30 youth undergoing orthopedic procedures with regional anesthesia, and 14 youth with sickle cell disease. Youth scheduled for surgery will undergo mechanical or thermal LQST and SA-QST before surgery in-person, and P-QST after surgery in the PACU, and every day up to three days postoperatively through telehealth. Youth with sickle cell disease will undergo LQST in-person and SA-QST in a virtual setting simulating at-home use. A questionnaire assessing the safety and tolerability of P/SA-QST will be completed. Five orthopedic surgery patients have completed the study since October 2024. No adverse events relating to P/SA-QST tool-kit were reported. Overall acceptability of P/SA-QST was high (median score of 49/50, range = 47-50). Our preliminary findings suggest that a P/SA-QST tool-kit may facilitate repeated sensory measures over time in studies of regional anesthesia, acute and chronic pain, nerve injury and neurologic diseases in a cost-effective and convenient manner, and therefore facilitate future research.

Pain Dismissal, Anxiety, Depression, and Substance-use Coping in Emerging Adults with Chronic Pain

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Twelve percent of emerging adults (EAs) experience chronic pain. Having one's pain dismissed is not uncommon and is isolating. The current study explores pain dismissal's relationship to anxiety, depression, and coping with substances. Undergraduate students with chronic pain (N = 229, age M = 19.58, SD = 1.42, range = 18-25) at a Midwestern university reported if they had pain, if their pain had been dismissed, their anxiety, depression, and substance-use coping. Most participants identified as women (86.0%) and BIPOC, or non-white (n = 132, 57.6%). EAs that experienced pain dismissal (n = 98) had higher anxiety scores (M = 12.87, SD = 5.74) compared to those that did not experience dismissal (n = 131, M = 11.26, SD = 5.62; t(227) = 2.12; p = .035). Those that experienced pain dismissal also had higher depression T-scores (M = 59.27, SD = 7.55) compared to those that did not experience dismissal (M = 56.44, SD = 8.59; t(227) = 2.60; p = .010). EAs that experienced pain dismissal did not differ in their use of substances to cope (M = 3.44, SD = 1.90) compared to those that did not experience dismissal (M = 3.19, SD = 1.74; t(227) = 1.03; p = .306). Having one's pain dismissed was related to higher anxiety and depression, but not substance use for coping. Reducing instances of pain dismissal and increasing validation of symptoms may decrease anxiety and depression in EAs with chronic pain.

Adverse Childhood Events (ACEs) Associated with Increased Acute Post-Surgical Pain Intensity in Adolescents in the United States

Sophia Kreider, Rebecca Flack, Jennifer Rabbitts, Tonya Palermo, Cornelius Groenewald; Stanford University

Recent research supports that youth with adverse childhood events (ACEs) are at increased risk for chronic pain during adolescence. Yet, the relationship between ACEs and acute pain remains poorly described. The primary aim of our analyses was to determine the associations between ACEs and acute pain intensity after surgery in adolescents in the United States. We hypothesized that a higher prevalence of ACEs would be associated with higher ratings of acute pain intensity. We analyzed preliminary survey data from 93 parent-child dyads with adolescents (10-19 years) undergoing outpatient orthopedic surgery. Youth completed 4 ecological momentary assessments (EMAs) per day for 14 days post-surgery, rating their pain intensity on an 11-point numeric rating scale (NRS, 0-10). Pain ratings were averaged to create a single score. ACEs scores were obtained from a 10-item parent-report questionnaire. Consistent with our hypothesis, the mean pain score was higher among patients with 1+ ACEs (3.0/1.6)(mean/sd) compared to those with 0 ACEs (2.4/1.4). However, a two-sample t-test did not demonstrate a statistically significant difference (p=0.0766). Linear regression showed that adolescents with 1+ ACEs reported higher post-surgery pain intensity (B=0.11, p=0.2868) compared to those with 0 ACEs after adjusting for demographics. These results suggest that ACEs are associated with acute pain intensity. Enrollment is ongoing, and further analyses on a larger sample will be presented at USASP to

inform effective interventions that prevent and reduce acute pain intensity post-surgery. Funding: R01HL166337.

Development of a Neuro Irritability Clinic to Improve Management of a Challenging Condition

Clare Riotte; University of Connecticut

Neuroirritability is a common presentation among pediatric pain patients yet literature to assist in the recognition and treatment of symptoms is limited. We sought to fill this gap by developing a subspecialty clinic to increase awareness and address the needs of this unique group of patients and their families. Neuro Irritability is defined as persistent or recurrent episodes of pain behaviors which, after assessment and management of potential nociceptive sources, can most likely be attributed to abnormal signaling of the central nervous system. Neuro Irritability is frequently associated with other comorbid conditions and can present at any time though patients most commonly present during the newborn period, at the onset of adolescence or in relation to neurotrauma that may happen later in life. We have created a subspecialty clinic to address unique presentations of complex patients experiencing neuro irritability and guide families toward an optimal management plan which often includes the use of gabapentin or clonidine. A guideline was created for community pediatricians to assist in management and a database was established in Redcap to collect relevant clinical information. Since its publication, the guideline was viewed 44 unique users and the clinic has served 25 patients with approximately 1 new referral per month. The number of guideline views since its publication supports its value to the broader community. By updating the guideline for pediatricians and collecting data as we grow our program, we hope to eventually establish data-driven recommendations for optimal management which could be disseminated into the broader pediatric community.

Peripheral Nerve Stimulation for Treatment Of Postoperative Neuropathic Pain Management

Vipin Bansal, Varun Goel, Brandon Hou; Emory University

Neuropathic and phantom pain following an amputation can be managed effectively with peripheral nerve stimulation (PNS), offering a new option for pediatric patients to minimize narcotics. In our treatment of a patient who underwent bilateral amputations of upper and lower extremities following ECMO due to septic shock, pain management was complicated by postoperative high dose narcotics, gabapentin, ketamine and methadone usage. Unfortunately, both residual limb and phantom pain were unresponsive to this regimen. Due to limited regional anatomy landmarks and poor wound healing at the amputation site, targeted muscle reinnervation was not an option. Likewise, a spinal cord stimulator was avoided due to concerns of neuraxial bleeding and infection. Dual percutaneous PNS leads were placed in one limb targeting the left femoral and sciatic nerves under ultrasound image guidance with motor or paresthesia verification as tolerated by the patient. The percutaneous leads were connected to a miniature wearable stimulator for the 2-month therapy period, after which the leads were removed at bedside. While the PNS was in place, the patient was weaned off all pain medications and had pain scores of 0-1 for both the implanted limb as well as other amputated extremities. Pain was

assessed monthly to one year after lead removal, with no indicated recurrent pain episodes. The successful use of novel PNS technology in our patient offers a viable option for long term chronic pain control for other pediatric patients, while completely avoiding any drugs that can compromise mental and physical balance in school age children.

A Single Center Review of Long-Term Lidocaine Infusion as an Adjunct for Refractory Pain Management in CICU Patients

Kathleen Cao1, Parker Hilliard, Vipin Bansal; Emory University

A Single Center Review Of Long-Term Lidocaine Infusion As An Adjunct For Refractory Pain Management In CICU PatientsPain management in pediatric critical care presents significant challenges due to various procedures, interventions, and clinical conditions that frequently cause pain and discomfort during hospitalization. In the intensive care unit (ICU), the primary approach to analgosedation for managing moderate to severe pain in pediatric patients relies heavily on the use of opioids and ketamine with few viable alternatives for cases of refractory pain. Lidocaine, recognized for its analgesia benefits since the 1980s, is commonly used as a local anesthetic and an antiarrhythmic agent in the pediatric (PICU) and cardiac ICU (CICU). Lidocaine has been demonstrated as an alternative for opioid-free anesthesia through systemic administration for short durations in the adult literature in reducing pain scores, but pediatric data of long-term lidocaine infusion use for refractory pain remains limited. At Children's Healthcare of Atlanta (CHOA), lidocaine infusions have been successfully implemented as an adjunct therapy for refractory pain management in a small cohort of long-term pediatric CICU patients. A retrospective review of electronic health records demonstrated reduction in pain scores and decreased opioid requirements following the initiation of lidocaine infusion. This innovative approach includes the crucial aspect of monitoring lidocaine levels during lengthy infusions to monitor efficacy and minimize side effects. These results highlight the potential for standardizing lidocaine use, along with lidocaine level monitoring, to effectively manage refractory pain and improve care for critically ill pediatric patients.

Experiences of Bullying and Headaches Among Children: A Cross-Sectional Analysis

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Bullying is a public health problem that increases the risk of poor social, educational, and health outcomes among youth. An additional public health concern, headache is the most frequent manifestation of pain in childhood. However, few studies have examined the relationship between experiencing bullying during childhood and headaches. This cross-sectional analysis used data from the 2022 United States National Survey of Children's Health to examine the association between being bullied and headache history among children 6-17 years of age. After removing children with missing values, we performed bivariate analyses of caregiver-reported information on headache and frequency of being bullied for 31,255 children. We used multivariate logistic regression adjusted for demographics and health comorbidities to examine the association between being bullied and headache. Of the 31,255 children, 13,329 (42.6%)

were bullied once or more over the prior year, and 4,258 (13.6%) were bullied multiple times a month. The prevalence of headache among all participants was 1,538 (4.9%). Among children who were not bullied, the prevalence of headache was 3.6% compared to 6.6% among children who were bullied at least once in the prior year. Being bullied was associated with higher odds of headache (aOR = 1.71, 95% CI = 1.52 - 1.91). However, increased frequency of experiencing bullying was not directly associated with greater odds of headache in a dose-dependent fashion. Children who were bullied had an increased risk of experiencing headaches. Future studies are needed to evaluate specific timelines surrounding bullying experiences in relation to development of headaches.

Psychosocial Factors and Interventions

Pain Self-Efficacy and Pain Catastrophizing as Predictors of Health Outcomes in Patients with Chronic Pain

Emma Raney, Dokyoung Sophia You, Samsuk Kim; Stanford School of Medicine

Pain catastrophizing, characterized by rumination and helplessness on pain, is a well-known predictor of poor health outcomes in chronic pain populations. Additionally, pain self-efficacy, the belief in one's ability to manage and cope with pain, is a known predictor for positive outcomes in this population. This study examined the predictive roles of pain catastrophizing and pain self-efficacy for pain-related and functional outcomes in chronic pain patients over a 3-month period. Participants with chronic pain (N=262, 65% female, 79% White, mean age = 58 years) completed self-reported measures, including the Pain Catastrophizing Scale (PCS), three Chronic Pain Self-Efficacy Scale for pain (CPSS-pain), activity (CPSS-activity), and coping with symptoms (CPSS-coping), and PROMIS measures for pain intensity, pain bothersomeness, and pain interference, and physical function. Multiple regression analyses, controlling for demographics (age, sex), revealed that higher PCS scores predicted greater pain intensity, pain bothersomeness, and pain interference ($\beta = 0.210–0.289$, $r2 = .032–.061$, $ps < .005$), while lower CPSS-pain ($\beta = -0.213–-0.201$, $r2 = .024–.049$, $ps < .016$) and CPSS-activity ($\beta = -0.339–-0.277$, $r2 = .038–.061$, $ps < .004$) scores were associated with worse pain outcomes. In contrast, greater physical function was predicted by higher CPSS-pain ($\beta = 0.199$, $r2 = .023$, $p = .004$) and CPSS-activity ($\beta = 0.664$, $r2 = .214$, $p = .114$), but not by PCS or CPSS-coping scores ($ps > .103$). These findings suggest that while pain catastrophizing and pain self-efficacy predict pain-related outcomes, only self-efficacy in managing pain and engaging in activity predicts physical function. Enhancing pain self-efficacy, particularly regarding activity, may be an effective intervention target to improve physical function in chronic pain patients. Redlich Endowment Fund

Emergency Department Utilization Among Individuals with Heterogenous Chronic Pain Enrolled in a Group-Based Activity Program

Julia Hooker, Jonathan Greenberg, Ana-Maria Vranceanu; Massachusetts General Hospital/Harvard Medical School

Chronic pain is highly prevalent, engenders a significant economic burden, and accounts for 10-16% of all Emergency Department (ED) visits. It is the most common chief complaint among

individuals with ≥6 annual ED visits, despite the fact that EDs are not well-suited to address the complex care needs of individuals with chronic pain. Given that patients continue to seek chronic pain care from EDs nationwide, examining clinical characteristics associated with ED utilization may serve to identify factors motivating ED presentation among this population. Here, we examine the clinical characteristics associated with ED utilization (vs no ED use) among individuals with chronic pain enrolled in a multisite feasibility RCT. Participants (N=92) were recruited from 3 medical centers for a larger, longitudinal study comparing a mind-body activity program (GetActive-Fitbit) with a health education comparison condition. Sociodemographic information, ED utilization, pain-related psychosocial functioning, and pain management data was collected across 3 timepoints. Of the 92 participants, 12% visited the ED for chronic pain care at least once during the study (22 total visits, Mage=62.6, 100% female). Preliminary results suggest that individuals who visited the ED demonstrated greater functional impairment, greater pain intensity, and higher pain catastrophizing compared to those without ED visits. These differences should be interpreted with caution due to the small size of the ED visit group. The present findings may improve our understanding of factors motivating individuals with chronic pain to seek pain care in the ED. Future work should explore the predictive value of these characteristics on ED utilization.

Pain, Altruism, and Decision-Making: The Influence of Social Context and Task Repetition on Behavior and Placebo Effects

Amin Dehghani, David Gantz, Tor Wager; Dartmouth College

We investigated human decision-making behavior in scenarios where individuals could choose to reduce either their own pain or someone else's, versus opting for personal financial gain, as well as how decisions of other anonymous participants impacted individual pain sensation. We utilized a decision-making task where participants chose to either accept or reject a monetary payoff that caused pain to themselves or another person, which was repeated two times. Additionally, experimenter-generated pain offers, deceptively presented as coming from other anonymous participants, were applied to examine the social transmission of placebo effects.Results from the decision-making task showed significant effects of pain ($T(198) = -13.8$, $p < 0.001$, higher pain offers increased probability of refusal), monetary value ($T(198) = 15.7$, $p < 0.001$, higher monetary offers increased probability of acceptance), and overall hyperaltruistic behavior by participants (Decision type $T(198) = 3.7$, $p < 0.001$, accepting more offers for self vs. others). However, this altruistic behavior was slightly decreased after repeating the decision-making task. Additionally, both pain ($F(1,66.8) = 24.1$, $p < 0.001$, higher pain offers by previous participants increased pain sensation) and monetary values ($F(1,188.4) = 4.6$, $p < 0.05$, higher monetary offers by previous participants increased pain sensation) offered by previous participants had a placebo effect on pain sensations reported by participants. This research sheds light on the balance between self-interest and altruism in moral decision-making, emphasizing the potential for hyperaltruistic behavior to emerge even within a predominantly self-centered framework.

Advancing the Science of Peer Support Interventions Will Require More Than the Usual Pain Endpoints

Rita Romero, Jennifer S. De La Rosa; University of Arizona Health Sciences

Contributing authors are collaborators on a program which uses a telehealth model to train, recruit and certify individuals in underserved communities as peer support specialists, building the peer pipeline while enhancing community capacity to address opioid use disorder (OUD). Our experience in training, implementing, and developing new roles for peer specialists, has honed our awareness of effective implementation as a necessary condition for peer success. Yet implementation factors seem to not often be reported in the academic literature on peers. We conducted a scoping review of literature (n=60) evaluating effectiveness of peer support for OUD to assess how often (1) role characteristics and (2) intervention characteristics are reported in the literature on effectiveness of peer support. Role characteristics include: e.g., payment of a living wage, full-time/part-time status, benefits-eligibility, size of peer staff, peer's years of experience, organizational experience employing peers, and peer supervisors' and clinical staff's belief in the value and service mission of the lived-experience workforce. Intervention characteristics include: whether a peer delivered intervention is clearly defined and mapped to logical outcomes, whether fidelity to it was monitored, and whether it was perceived as feasible and acceptable by service recipients, peers, and clinical staff. Although 67% of publications made a determination on the effectiveness of peer support, only 33% of reported any implementation characteristics. None evaluated fidelity to a defined peer-delivered intervention. The lack of implementation information limits advancement of the evidence-base around this exciting workforce and the unique opportunities they provide in support of those living with pain.

Decoding Sentiments of Injustice in Chronic Pain: A Natural Language Processing Approach with roBERTa

Dylan Coe, Cassie Yu, Junfeng Ma, Marie Meyer, Sisi Li, Rita Dinh, Lucent Chang; University of Wisconsin-Madison

Effective communication between providers and patients is crucial for successful chronic pain treatment (Smith et al., 2022). However, patients often find it challenging to voice their experiences authentically, particularly when they involve feelings of perceived injustice (Johnson & Williams, 2023). Online forums such as r/ChronicPain, r/Fibromyalgia, and r/backpain on Reddit provide relatively anonymous spaces where individuals can express unvoiced frustrations and seek advice (Rodriguez, 2021). Leveraging machine learning and natural language processing techniques, this study examines sentiments of perceived injustice expressed in these forums to enhance understanding of these emotions in patient-provider communication. We collected, labeled, and analyzed over 1,000 posts from chronic pain-related subreddits on Reddit in 2022. Using this dataset, we trained a Robustly Optimized Bidirectional Encoder Representations from Transformers Approach (RoBERTa) model to classify posts based on common sentiments of pain injustice: "blame," "loss," "invalidation," "hopelessness," and "fear" (Chen & Liu, 2023). Results demonstrate that RoBERTa outperforms alternative classification methods, such as Naive Bayes, in accurately categorizing these sentiments (Thompson et al., 2022). Additionally, the model provided insights into language patterns, offering interpretable classifications for each category. These findings suggest that natural language processing models like RoBERTa could play a vital role in detecting sentiments of perceived injustice, enabling

healthcare providers to address patients' emotional and psychological needs. This novel application of machine learning in pain science may guide the development of tools that foster empathetic communication and advance equitable, personalized care for individuals with chronic pain.

Disease Self-Efficacy, Not Self-Reported Fatigue, is Associated with 1-Minute Sit-to-Stand Performance in People with Migraines

Brandon L. Boring, John Gunstad, Karin G. Coifman; Kent State University

Disease self-efficacy in people with migraines predicts favorable health outcomes including quality of life and well-being. However, it has not been explored in relation to fatigue - a frequently reported symptom experienced by those with migraines. Presence of fatigue is quantifiable using exercise tests including the 1-minute sit-to-stand task (1MSTS), with people with migraines having previously shown to perform worse relative to healthy controls. Here, using data from the Kent State Student Life Study, we assessed the association between disease self-efficacy, self-reported fatigue, and performance on the 1MSTS hypothesizing that greater self-efficacy would be positively associated with task performance, while self-reported fatigue would be negatively associated with performance. We found that people with migraines ($n = 33$) showed significantly greater self-reported fatigue compared to those without, matched by age, sex, and BMI ($n = 29$), $t(60) = 3.65$, $p < .001$, 95% CI [.679, 2.322], but surprisingly also performed significantly better on the 1MSTS as indicated by number of full repetitions, $t(54) = 3.45$, $p < .001$, 95% CI [3.473, 13.094]. Within people with migraines, greater disease self-efficacy was positively associated with 1MSTS performance $r = .488$, $p = .008$, whereas self-reported fatigue was not $r = -.056$, $p = .780$. Findings provide evidence for the role of disease self-efficacy as indicated by an objective marker of physical functioning and fatigue, identifying a potential maker for clinical intervention to help support the health and well-being of people suffering from migraines.

"How Am I Supposed to Relax?": A Qualitative Analysis of Pain Experiences in Autistic Adults and Their Relationship to Healthcare Interactions.

Joey Shapiro, Amy Watson-Grace, Ankita Patel, Kaitlin Kuhlman, Nathan Haid, Alexandra Strum, Carissa Cascio, Michelle Failla; The Ohio State University

Differences in communication and sensory processing are core autistic features that may impact autistic people’s experiences in healthcare. Previous studies document that autistic adults may not fully benefit from their healthcare interactions due to communication breakdowns, exacerbating health disparities. We interviewed autistic adults about their pain communication and sensory issues, hypothesizing that pain communication and sensory differences may contribute to subjectively less beneficial healthcare for autistic adults. A subsample of 10 autistic adults were interviewed following participation in a pain psychophysics study. A codebook was iteratively developed to thematically analyze interviews that asked questions about pain experiences, sensory differences, and healthcare interactions. Themes were identified around pain communication, sensory issues, and pain-related anxiety. Autistic adults reported that they didn't feel medical professionals asked about pain adequately, “they never really ask.” Pain

anxiety was described specifically around medical procedures and a distrust of the medical provider around pain expectations, “I was told it wouldn’t hurt at all.” Pain and sensory sensitivities seemed to interact with anxiety; one person stated that “anything with anxiety involved or if I'm getting sensory overload” impacted their pain experience. Accommodations for communication, “I like the faces scale,” and sensory stimuli, “they allow me to wear earbuds and play some calming music, so that really helps,” were reported as ways to improve patient experience. Many autistic adults reported avoiding the doctor altogether, “I hate going to the doctor.” These findings suggest that targeting accommodations around pain communication and pain-related anxiety may improve healthcare interactions for autistic adults.

Bondage-Discipline, Dominance-Submission, and Sadism-Masochism Fantasies, Behaviors, and Identification Predict Pain Slopes Across Time in a Cold Pressor Test
Ashley Palmateer, Benjamin Van Dyke; Young Harris College

Bondage-Discipline, Dominance-Submission, and Sadism-Masochism Fantasies, Behaviors, and Identification Predict Pain Slopes Across Time in a Cold Pressor TestAshley N. Palmateer and Benjamin P. Van Dyke; Young Harris CollegeDespite potentially valuable insights into different ways of relating to pain offered by research involving practitioners of bondage-discipline, dominance-submission, and sadism-masochism (BDSM), minimal research has heretofore examined pain in that community. The current study seeks to address this gap and expand upon our previous findings through a more nuanced examination of pain response in relation to BDSM experience, attitudes, and identity. We conducted a secondary data analysis using linear growth models with repeated measures of cold pressor pain ratings (taken every 30s up to pain tolerance or a naïve ceiling of 5 minutes) nested within individuals to determine if BDSM variables predict pain slopes across time during the cold pressor task (2-4 degrees Celsius). Results indicated that endorsing more fantasies about rough sex and degradation/humiliation predicted significantly faster increases in pain ratings during the cold pressor task, whereas fantasies about domination/sadism, self-reporting relinquishing power during sex, and identifying with the BDSM community predicted significantly slower increases in pain ratings. These findings provide preliminary evidence for how BDSM attitudes and experiences relate to pain processing and sensitivity in a more dynamic way during a single painful event, highlighting how attitudes, experiences, and potential community identification may shape or be shaped by pain perception and tolerance. Funding sources: The Appalachian College Association Ledford Scholarship Program and the Young Harris College Undergraduate Research Program.

The Relationships Among Negative Affect, Concerns about Pain, Applied Mechanical Pain, and Physical Activity
Lorin Tidick, Lauren Cooper, Benjamin Van Dyke; Young Harris College

The Relationships Among Negative Affect, Concerns about Pain, Applied Mechanical Pain, and Physical ActivityLorin E. Tidick, Lauren E. Cooper, and Benjamin P. Van Dyke; Young Harris College Emerging adults are reporting increasing levels of stress, which could affect how they respond to the pain of a potential injury. This study aims to examine how negative emotions might affect pain and the ability to engage in physical activity after perceived injury. We tested

an exploratory hypothesis that college students who report higher levels of negative affect will report higher levels of pain while physical active. The participants for this study were undergraduate students who were at least 18 years old. Participants completed a series of questionnaires before and after two sessions of physical activity on a treadmill. Between treadmill tests, researchers applied mechanical pressure to the right medial femoral tubercle at one of two randomized pressure levels (1-3 or 13-15 lbf) using an algometer to simulate possible injury pain. Correlations suggest that people who have more situational concerns about pain immediately after a perceived injury have more negative affect in response to physical activity and those who have more negative emotions in response to physical activity report higher levels of pain during physical activity (medium to large effects). This study highlights how concerns about pain can affect response to perceived injury among emerging adults, potentially highlighting future targets of intervention post-injury. Funding sources: The Appalachian College Association Ledford Scholars Program and the Young Harris College Undergraduate Research Program.

Relationships Among Grit, Physical Performance, and Response to Perceived Injury Using Applied Mechanical Pain
Lauren Cooper, Lorin Tidick, Benjamin Van Dyke; Young Harris College

Relationships Among Grit, Physical Performance, and Response to Perceived Injury Using Applied Mechanical PainLauren E. Cooper, Lorin E. Tidick, and Benjamin P. Van Dyke; Young Harris CollegeAthletes commonly perform at high levels despite injury or pain, which might increase risk for long-term injury and chronic pain and might be a result of having higher levels of grit, or passion and perseverance for long-term goals. The aim of this study was to evaluate how grit affects response to perceived injury pain. We hypothesized that participants with higher grit would demonstrate higher physical performance after simulated injury pain. Participants were undergraduate students who were 18 years and older. After completing the Short Grit Scale, participants ran on a treadmill for 2 minutes at 75-80% max effort. Next, researchers applied mechanical pressure to the participant's right medial femoral tubercle at one of two randomized pressure levels (1-3 or 13-15 lbf) using an algometer. Finally, participants completed a second treadmill test. Results indicated a small positive correlation between grit and distance run after pressure pain application; large positive correlations between grit and being a collegiate athlete and likelihood to tell someone about pain/injury; and large negative correlations between grit and likelihood to conceal pain/injury and likelihood to push through pain. This pattern of findings tentatively suggests grit might help athletes better meet their long-term goals by helping them self-regulate appropriately in response to perceived injury. Funding sources: The Appalachian College Association Ledford Scholars Program and the Young Harris College Undergraduate Research Program.

Experimental Pain Response Among Sexual and Gender Minority Members Who Do and Do Not Practice Dominance-Submission and Sadism-Masochism
Veronica Lee, Ashley Palmateer, Benjamin Van Dyke; Young Harris College

Experimental Pain Response Among Sexual and Gender Minority Members Who Do and Do Not

Practice Dominance-Submission and Sadism-MasochismVeronica A. Lee, Ashley N. Palmateer, and Benjamin P. Van Dyke; Young Harris College Sexual minority people are more likely to engage in bondage-discipline, dominance-submission, and sadism-masochism (BDSM) than heterosexual people. Although the relationship between sexual minority identification and BDSM has been explored, it has not been adequately addressed regarding pain. This study aims to investigate how sexual minority identification and specific BDSM behaviors relate to experimental pain responses. This exploratory study is a secondary data analysis of a study in which participants completed a cold-pressor task (2-4 degrees Celsius) and monofilament sensory testing using 300g (6.65) von Frey filaments. Correlation results revealed a nonsignificant trend toward transgender participants tolerating less cold pain and demonstrating more temporal summation of pain compared to cisgender participants. Significant interactions revealed that sexual minority participants who had never practiced submission during sex reported less cold pain than sexual minority participants who had practiced submission or heterosexual participants who had not. Additionally, heterosexual participants who had never practiced sexual domination reported significantly more cold pain than heterosexual participants who had or sexual minority participants who had not. These results add to a growing literature on sexual and gender minority members' pain experience and suggest that the effects of BDSM on pain response might depend on sexual minority group membership. Funding sources: The Appalachian College Association Ledford Scholars Program and the Young Harris College Undergraduate Research Program.

Examining Community Integration as a Mediator Between Injury-Related Stigma and Pain Interference Following Burn Injury

Clara O'Brien, Shelley Wiechman, Arjun Bhalla; University of Washington School of Medicine

Injury-related stigma has been found to be associated with greater pain interference in burn survivors. From a cognitive-behavioral perspective, social integration in one's community can play an important role in challenging stigma, and social activity outside the home is associated with less pain interference (PI). However, stigma is often found to be associated with worsened social engagement. Thus, we sought to examine community integration (CI) as a mediator between stigma and PI. Data were pulled from the publicly available Burn Model System (BMS) National Data and Statistical Center. Participants included 485 adults who had experienced moderate-to-severe burn injury. At 6-months after injury, participants completed self-report measures assessing stigma (NeuroQOL Stigma scale), CI (Community Integration Questionnaire - Social Only) and PI (PROMIS Pain Interference-Short-form). Mediation analysis was conducted using the lavaan package (v 4.4.2) in R. We found stigma to be associated with both CI ($B = -.24$, $p < .001$) and PI ($B = .38$, $p < .001$), and CI to be associated with PI ($B = -.29$, $p < .001$). Additionally, the indirect effect was statistically significant ($B = -.09$, $p < .001$), however, a direct association between stigma and PI remained significant ($B = -.29$, $p < .001$). As individuals experience greater stigma, they become less integrated in their community and report greater pain interference. Findings suggest that individual interventions that target burn survivors' CI may support their pain outcomes, even in the face of stigma, however, systemic interventions to reduce stigma continue to be important.

Treatment Mediators of Sleep Improvement after Skills-based Behavioral Interventions for Chronic Low Back Pain: A Secondary Analysis of a Randomized Clinical Trial
Samsuk Kim, Dokyoung Sophia You, Sean Mackey, Beth D. Darnall; Stanford University School of Medicine

Sleep disturbance is common among individuals with chronic low back pain. Skills-based behavioral pain interventions have significantly improved sleep even when treatments contain minimal or no content directly targeting sleep. However, treatment mechanisms underlying sleep improvements remain unclear. This secondary mediation analysis tested the hypothesis that the treatment effect on sleep is explained by improvements in pain processing variables (e.g., catastrophizing), pain-related symptoms, and emotional distress. We randomized adults with chronic low back pain to either a skills-based behavioral intervention (8-session Cognitive Behavioral Therapy for Pain or 1-session Empowered Relief; N=123) or a no-skills 1-session education control (N=57). Participants completed surveys at baseline and at 1-, 2-, and 3-months post-treatment, assessing sleep disturbance, pain processing variables (pain catastrophizing, self-efficacy, and acceptance), pain-related symptoms (pain, pain interference, physical function, fatigue), and emotional distress (depression, anxiety). Our results indicated that the skills-based interventions were superior to control for reducing sleep disturbance at 3-month post-treatment ($p<.001$; moderate effect $\eta^2p =.09$); also, this sleep improvement was mediated by improved pain processing variables, not by improved pain-related symptoms and emotional distress. Among the pain processing variables, only the reduction of pain catastrophizing was a significant treatment mediator ($\beta=1.61$; CI [0.57, 3.09]). Our findings highlight that reductions in pain catastrophizing mediate sleep improvements following skills-based behavioral interventions. This underscores the critical role of targeting maladaptive pain processing to enhance sleep quality in individuals with chronic low back pain. Future research should focus on integrative treatments that address both pain and sleep disturbances to optimize patient outcomes.

The Influence Of Psychosocial Factors On Nociplastic Pain In TMD
Barquiesha Madison, Alia Lawhorne, Daniel Harper, Ashley Gagnon; Augusta University/University of Georgia Medical Partnership

Historically, psychosocial factors were viewed as secondary responses to pain. New insights reveal that these factors influence the onset, persistence, and severity of chronic nociplastic pain, i.e. pain from altered nociception without tissue damage, as seen in temporomandibular disorder (TMD). This study aimed to 1) compare the presence of psychosocial factors in TMD patients and pain-free controls and 2) evaluate the link between nociplastic pain and multimodal hypersensitivity in TMD patients.TMD patients (n=30) and pain-free controls (n=24) completed psychosocial questionnaires assessing psychosocial status. Visual, thermal, auditory, and pressure sensory testing was conducted at the temporomandibular joint, masseter, forearm, hand, and leg. Group differences were analyzed using SPSSv29.0 with t-tests and non-parametric tests. Bivariate associations between psychosocial factors, nociplastic pain, and sensory sensitivity were examined, with a level set to $p<.05$.TMD patients had significantly higher anxiety, FM-ness, jaw function limitation, hypervigilance, catastrophizing, negative affect, physical dysfunction, fatigue, sleep disturbance, and kinesiophobia. Depression, positive affect, perceived

stress, and hyperacusis showed no significant difference. In TMD patients, nociplastic pain which is measured by FM-ness, i.e. the extent of fibromyalgia-like symptoms, was associated with poorer psychosocial status. TMD patients also had higher visual and auditory sensitivity, correlating positively with nociplastic pain.TMD patients experience more psychological distress than pain-free controls. Elevated nociplastic pain in TMD patients is linked to increased psychological distress and multimodal hypersensitivity. These findings suggest that TMD patients with higher nociplastic pain and psychosocial dysfunction may need specialized treatments beyond standard nociceptive pain management. Funding: NIDCR Grant#R00 DE026810-05.

The Moderating Role Of Depressive Symptoms On The Association Between Adverse Childhood Experiences And Placebo Analgesia

Belina Rodrigues, Indraja Meizys, Lakota Watson, Nandini Raghuraman, Titilola Akintola, Luana Colloca; University of Maryland

An increasing body of research has been focusing on interindividual differences in placebo analgesia, exploring the potential influence of past experiences and related conditions such as depressive symptoms. In this study, we investigated the relationship between Adverse Childhood Experiences (ACE) and placebo analgesia, specifically examining whether this relationship is mediated by depressive symptoms. To address this question, we recruited 401 participants with Temporomandibular Disorder (TMD). The placebo manipulation involved two conditioning blocks and one testing block. During conditioning, maximum and minimum pain temperatures were paired with red and green screens, respectively, while the testing phase used a moderate pain temperature paired with both screens. Pain intensity was rated after each stimulation using a 100-point Visual Analog Scale (VAS). ACEs were assessed using the Adverse Childhood Experience International Questionnaire, and depressive symptoms were measured with the PHQ-9. We observed that higher ACE scores were associated with a greater reduction in placebo analgesia. This effect of ACE on placebo analgesia was independent of depressive symptoms (95% CI: [-1.38, -0.09], $p = 0.028$). Additionally, depressive symptoms, as measured by the PHQ-9, exerted a significant indirect effect (95% CI: [-0.38, -0.04], $p = 0.012$). Thus, depressive symptoms mediate the relationship between ACE and placebo analgesia. Specifically, PHQ-9 scores contributed significantly to the negative relationship between ACE and placebo analgesia. These findings suggest that depressive symptoms play a significant role in mediating the impact of ACE on placebo analgesia, contributing to a better understanding of the mechanisms underlying interindividual differences in placebo responses.

Depressive Symptoms and Their Influence on Pain Evoked During Visual Light Discomfort Threshold Testing in Patients with Chronic Ocular Pain

Cameron Talbert, Vanda Faria, Nicholas J Pondelis, David Valdes, Ema Karakoleva, Paula A Sepulveda-Beltran, Mariela C Aguilar, Heather Durkee, Alex Gonzalez, Jean-Marie Parel, Deborah S Jacobs, Joseph B Ciolino, Elizabeth R Felix, Anat Galor, Eric A Moulton; Boston Children's Hospital

Depression has been associated with heightened pain report in some chronic pain cohorts, but the

association between depressive symptoms and measures of evoked pain sensitivity is dependent on several factors, including stimulus modality. We investigated whether pain thresholds evoked by visual light stimuli differed between individuals with chronic ocular pain (COP) with low vs high depressive symptomology. Participants with COP (average eye pain level ≥1 in the past week, duration ≥3 months) were recruited from Boston and Miami clinics. We assessed depressive symptoms using the PROMIS-shortform Depression 4a questionnaire (Dep4a) and measured visual photosensitivity threshold (VPT) with the Ocular Photosensitivity Analyzer using the methods of limits, where participants indicated when the light intensity was uncomfortable to view. Ratings of pain intensity and the unpleasantness of the sensation at VPT was also captured using visual analog scales (0-100mm). 25 participants with COP (mean 49.1±17.7yo, 14Males:11Females) were divided into low (LowDep) and high (HighDep) depressive symptom groups based on a median split of Dep4a scores. An unpaired t-test showed no significant difference in VPT between groups ($t(23)= 0.443$, $p= 0.33$; LowDep= 1.82 ±1.12 log lux, HighDep= 1.62± 1.17 log lux). Significant differences were detected in VAS ratings of pain intensity ($t(23)= -2.26$, $p= 0.017$; LowDep= 23.2±25.7, HighDep= 47.8±28.7) and unpleasantness ($t(23)= -2.165$, $p= 0.02$; LowDep 46.8±24.0, HighDep 67.2±23.0). These findings suggest that depressive symptoms in patients with COP are associated with increased report of pain intensity and unpleasantness sensations from light stimuli, despite no effect on VPT.

Potentially Morally Injurious Events, Pain Experiences, and Functioning in Post-9/11 U.S. Veterans

Marcus G. Wild, Dustin Greer, Sheila F. O'Brien; Veterans Integrated Services Network 17 Center of Excellence for Research on Returning War Veterans

Moral injury—the lasting psychological harm characterized by guilt, anger, and shame that results from violations or betrayals of right and wrong—is associated with worse psychological and functional outcomes. The relation between moral injury and chronic pain, however, is under-investigated. No study has yet investigated the longitudinal associations of moral injury with pain outcomes, nor compared how moral injury and posttraumatic stress disorder (PTSD) symptoms contribute to pain experience and psychosocial functioning. We hypothesized that potentially morally injurious events (PMIEs)—experiences of either acts that were wrong or betrayal—and PTSD symptoms would be positively correlated both cross-sectionally and prospectively with pain intensity, and negatively correlated with functional disability. We conducted secondary data analysis in a sample of 351 post-9/11 U.S. veterans (70% male, 33.6% Black/African American) who completed baseline and 2-year assessments. Betrayal, but not wrongs, was cross-sectionally associated with pain intensity (ρ=0.19, 95% CI:0.07-0.30); both were cross-sectionally associated with functional disability (betrayal: ρ=0.39, 95% CI:0.30-0.48; wrongs: ρ=0.36, 95% CI:0.27-0.45). Neither wrongs nor betrayal were longitudinally associated with two-year pain intensity; however, both were related to two-year functional disability (betrayal: ρ=0.39, 95% CI:0.29-0.48; wrongs: ρ=0.39, 95% CI:0.29-0.48). PTSD symptoms at baseline were more closely associated with pain intensity both cross-sectionally (ρ=0.38, 95% CI:0.27-0.49) and prospectively (ρ=0.15, 95% CI:0.01-0.28) than PMIEs. Results suggest avoidance and negative alterations of cognitions and mood may impact subsequent pain intensity

more than events that violate moral beliefs, and events that violate moral beliefs may associate with functional disability more than pain intensity.

Generation Isolated: The Hidden Pain of Pandemic Loneliness in Young Adults
Montae Bermudez, Asad Ansari, Klarissa Lopez, Diya Dharmendran, Brandon Boring, Vani Mathur; Texas A&M University

Generation Isolated: The Hidden Pain of Pandemic Loneliness in Young AdultsMontae E. Bermudez, Asad Ansari, Klarissa L. Lopez, Diya Dharmendran, Brandon L. Boring, Vani A. MathurTexas A&M UniversityLoneliness is increasingly recognized as a social determinant of health across the lifespan, but also one that disproportionately impacts young adults. Loneliness surged in 2020 due to widespread social isolation during the COVID-19 pandemic. While previous research suggests that loneliness exacerbates the pain burden among individuals with chronic pain, its association with increased pain burden among young adults remains unclear. To address this gap, 704 college students (M age = 18.67, SD = 0.993; 61.2% identified as women and 73.2% white)—94 with chronic pain and 610 without—were recruited between October and November 2020, to complete an online survey of pain and loneliness. Across participants, loneliness was associated with self-reported central sensitization (CSI) and present pain intensity (BPI). Regression analyses revealed that, even after accounting for demographics, depression, and anxiety, loneliness significantly predicted CSI, but not BPI. Within group regressions revealed that loneliness independently predicted CSI (controlling for covariates) among participants without chronic pain, but not among those with chronic pain. Though future research is needed, this work indicates that loneliness is linked with pre-clinical central sensitization, and may be a risk factor for the development of chronic pain. Considering the unique vulnerabilities present in the present cohort of young adults, future studies should explore potential cohort effects that may persist into later stages of life.

Towards Culturally Adapting a Psychological Intervention for Pediatric Functional Abdominal Pain in Spain: A Systematic Review
Jocelyn Zuckerman, Rocío de la Vega, Manasi Kulkarni, Adrián Fernández-González, Elena R. Serrano-Ibáñez, Natoshia R. Cunningham; Michigan State University

Functional abdominal pain disorders (FAPD) are among the most common chronic pain conditions of childhood worldwide. In Spain, approximately 20% of youth meet criteria for FAPD, and may experience significant pain-related impairment. Mental health comorbidities (e.g. anxiety disorders) are common and are associated with increased functional impairment. Cognitive behavioral interventions, including the “Aim to Decrease Anxiety and Pain Treatment” (ADAPT; a 6-session mixed in-person/virtual weekly program), have been shown to be effective in improving functional disability and anxiety in children with FAPD in the United States. The program has been adapted for children with FAPD in Swedish primary care settings; however, the approach has not been refined for use in Spain, despite the great need given the lack of available behavioral health providers for pediatric pain management. A cultural adaptation process of refining ADAPT for use in Spain, based on the Ecological Validity Model, is a critical

step toward creating a relevant intervention approach. The first step of this process is conducting a systematic review to identify areas of potential intervention refinement, which is the aim of this current research. Covidence software was used to screen manuscripts from Medline, Embase, and PsycInfo databases. This review identified and synthesized local characteristics of Spanish youth with FAPD that should be accounted for when refining the ADAPT protocol for use in Spain. Our preliminary results suggest dietary modifications (e.g., Mediterranean diet) and self-paced digital platforms are potential areas for refinement of ADAPT. Future directions include co-developing a culturally refined protocol for testing.

Assessing Opioid Stigma: Integrating Community Perspectives in Measure Development
Sarah Orris, Anna Gogiberidze, Justin Scott, Yael Schenker, Jessica Merlin, Hailey Bulls; University of Pittsburgh

Prescription opioids are standard of care for moderate-to-severe painful cancer. However, patients may face stigma associated with their use of prescribed opioids, or "opioid stigma". Currently, no validated tools exist to assess opioid stigma, limiting our understanding of its causes and consequences. Engaging stakeholders in the validation process ensures that assessment measures reflect the perspectives of people with lived experience. Thus, this study aimed to integrate community feedback in the preparation of an opioid stigma questionnaire prior to validation in patients with advanced cancer. We worked with the University of Pittsburgh CTSI Community PARTners team to create a Community Engagement Studio (CES), in which community members are invited to provide feedback on key research questions. The CTSI recruited 7 community members who endorsed direct lived experience with advanced, painful cancer; though participants did not provide sociodemographic information, CTSI prioritized community recruitment from populations at higher risk for pain undertreatment, including women and people of color. During a virtual 2-hour session, participants reviewed and refined a preliminary draft of the opioid stigma. Three primary themes emerged: 1) ensuring person-first language, 2) acknowledging the emotional burden of opioid stigma, and 3) adding new content to assess alternative pain management strategies. Integrating feedback from the CES was an essential step toward ensuring the future opioid stigma questionnaire reflects community perspectives and preferences. In the next phase, the validation of this measure will allow us to quickly and accurately assess opioid stigma in patients with advanced, painful cancer for future intervention development. NCI (K08CA263317).

N2-P2 Magnitude is Related to Trait Anxiety, but Not to State Anxiety During Measurement of Laser Evoked Potentials (LEPs)
Daniel-Ashley Lindo, Mark Saffer, Timothy Meeker; Morgan State University

Anxiety and pain are intimately intertwined. High trait anxiety predisposes people to develop chronic pain syndromes. Anxious anticipation exacerbates acute pain intensity. Mechanisms of augmentation of pain perception by anxiety remain unclear which is a barrier to reliable analgesic and anxiolytic therapies. Pain frequently signals impending tissue damage, which may be threatening. Discrimination of pain intensity indicates the threat magnitude of acute noxious stimuli. We have reported that high trait anxious participants have longer reaction times and

impaired task performance during pain discrimination. To explore the interaction between pain and anxiety we elicited laser-evoked potentials (LEPs) in 20 (7F) participants aged 19-66. A 1340 nm wavelength laser was applied to the distal half of the dorsal forearm and dorsum of the hand. Laser parameters included a 10mm-diameter beam with 20ms-pulse duration and energies ranging from 10J to 15J (fluence=12.74 to 19.11 J/cm2). Evaluating the relationship between the N2 and P2 magnitude of the LEPs with state and trait anxiety, we found trait anxiety was correlated with N2 and P2 magnitude (N2: R=0.62; p=0.0038; P2: R=0.53; p=0.015), while state anxiety was not correlated with N2 or P2 magnitude (N2: R=0.33; p=0.16; P2: R=0.24; p=0.31). These findings, which have previously been demonstrated in patients with tension-type headache, show that healthy participants with high trait anxiety, naïve to laser stimulation, also have enhanced top-down attentional capture of painful stimuli relative to those with low trait anxiety. However, this is not the case for state anxiety measured in the same session before laser exposure.

Pupillary diameter better anticipates painful conditioned stimulus than skin conductance response in a trace conditioning paradigm

Mark Saffer, Timothy Meeker; Morgan State University

Fear conditioning is a learning paradigm where a neutral stimulus becomes associated with an aversive stimulus. This association produced by the pairing of these stimuli leads to a psychophysiological response to the neutral stimulus, like that produced by the aversive stimulus, even when presented by itself. This psychophysiological response is most often observed by recording skin conductance, a measure of arousal. The latency of a skin conductance response (SCR) typically ranges between 1 to 3 seconds after presentation of a stimulus. This delayed response is due to the time to detect a change in SCR related to a preceding activation of sweat gland and is subject to individual differences. Pupillometry has also been used to assess fear conditioning. Pupil dilation to an aversive stimulus begins within 300 ms and peaks between 1-2 s and is dependent on the stimulus intensity and individual differences. Here we used a trace delay fear conditioning paradigm to compare SCR and pupillometry responses as measures of the physiological response to a painful aversive stimulus produced by a short duration (20 ms) laser pulse. In a trace delay paradigm the aversive stimulus is delivered after the neutral stimulus. Anticipation of pain is reflected in the physiologic response to the impending aversive stimulus. While both SCR ($t=-8.16$, $p<.0001$) and pupil dilation ($t=-7.09$, $p<.0001$) were measurable in response to an aversive stimulus reflecting the experience of pain, pupil dilation ($t=-4.79$, $p<.0001$) was more sensitive to the expectation of pain from the aversive stimulus compared to SCR (ns).

Exploring The Analgesic Effects Of Personally Meaningful Positive Music In An Affective Pain Modulation Task

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Various types of music have been used to modulate affect and pain in experimental paradigms. Such paradigms have translational potential because of the utility of music therapy for acute and chronic pain. This study investigated the effects of personally meaningful positive music, relative to standardized negative music and neutral noise, on pain intensity and unpleasantness among healthy volunteers (N = 44). Participants were exposed to 60-second music clips of positive, negative, and neutral valence in an order-randomized block design. Painful heat (i.e., Pain50) was applied to the ventral forearm at the midpoint of each music clip and participants rated pain intensity/unpleasantness following each trial. Trait positive and negative affects were also assessed. Linear mixed effects models revealed that, relative to the neutral condition, positive music significantly inhibited pain intensity and unpleasantness and negative music significantly facilitated pain unpleasantness (p's < .05). Positive and negative music were equally arousing, whereas neutral noise was rated as moderately calming, suggesting that arousal is not an independent contributor to music induced analgesia. Exploratory analyses indicated no evidence for moderation of experimental effects by affective traits (p's > .05). Overall, these findings demonstrate that positive personally meaningful music produces greater analgesia than calming neutral sounds. Future work will seek to uncover the role of personal meaning in music-based affective pain modulation by manipulating both the meaningfulness and the valence of music.
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Frequency and Correlates of Physical Activity among Young Adults with Chronic Pain
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An estimated 8.5% of US young adults experience chronic pain, and physical inactivity is a risk factor for worse pain outcomes. Given the scant literature characterizing physical activity (PA) in this population, this secondary analysis examined the frequency and psychosocial correlates of PA among young adults with chronic pain. Young adults (N = 129, 70.5% female, age 18-24) were recruited as part of a longitudinal study. Minutes per day of moderate to vigorous physical activity (MVPA), walking, and sedentary activity were assessed using the IPAQ-SF. Kinesiophobia, experiential avoidance, depression, anxiety, sleep disturbance, and fatigue were each independently tested as cross-sectional correlates of PA using generalized linear models with bootstrapped 95% confidence intervals. Models were adjusted for gender and past two-week pain severity. Median MVPA and walking time were 51.43 (IQR = 16.88- 100.71) and 90.00 (IQR = 42.86, 153.21) minutes/day, respectively. Average sedentary time was 384.06 minutes/day (SD = 150.23). Experiential avoidance (B = -.012, CI = [-.019, -.007]), depression (B = -.052, 95% CI = [-.100, -.017]) and fatigue (B = -.023, 95% CI = [-.514, .263]) were negatively associated with MVPA. Depression (B = 7.44, 95% CI = [1.37, 13.71]) was positively associated with sedentary time. There were no significant walking correlates. On average, this sample of young adults with chronic pain met current adult guidelines for MVPA (30 minutes per day) and were not dangerously sedentary (> 8 hours/day). Psychosocial factors that negatively impact activity level, particularly depression, may be important targets of intervention in this population.

Feedback and Perceived Similarity Enhance Accuracy of Pain Assessment Based on Facial Expression

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Feedback (Blanch-Hartigan et al., 2012) and perceived similarity between observer and observed (Yan et al., 2016; Elfenbein & Ambady, 2003) influence emotion recognition. However, their roles in pain assessment remain largely unclear. We hypothesized that feedback and perceived similarity would enhance pain recognition and learning. Forty-seven participants observed videos of other individuals undergoing thermal stimulation at varying intensities. In one task, observers rated whether the individual was in pain, and in a second task they estimated pain intensity. The Feedback Group (n = 23) were shown actual pain ratings after each rating, while the No-Feedback Group (n = 24) rated pain without feedback. At the end of the study, participants rated their perceived similarity to each individual. Linear mixed models revealed main effects of Group, such that feedback significantly improved accuracy in both tasks (ps < 0.05). We also observed a Group x Trial x Block interaction ($\beta = -0.052$, $p = 0.036$), such that the Feedback Group showed larger changes in accuracy of categorical judgments (pain/no pain) over time ($\beta = -0.047$, $p = 0.010$). Perceived similarity also significantly enhanced accuracy in both tasks (ps < 0.005) and interacted with Group in pain intensity assessments ($\beta = 0.095$, $p = 0.044$), such that perceived similarity was associated with improved accuracy only in the No-Feedback Group ($\beta = -0.122$, $p = 0.001$). These findings demonstrate that feedback and perceived similarity impact pain assessment accuracy and social learning, offering insights for training protocols that integrate feedback and sociocultural factors for clinical applications.

Perceived Socioeconomic Status as a Moderator of the Relationship between Pain Coping Strategies and Pain-Related Experiences

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Understanding individual differences in pain coping is essential to personalizing pain treatment. Recent literature shows that pain coping strategies are not a “one size fits all;” rather, individual and cultural factors impact the success of specific emotion regulation strategies. The current study tested whether perceived SES, a personal assessment of one’s social, economic, and educational standing within society, moderated relationships between pain coping strategies and pain severity and pain interference. Adults (N = 1453) with chronic pain completed measures of perceived SES (U.S. MacArthur Scale of Subjective Social Status), pain coping (Coping Strategies Questionnaire), and pain related-experiences (Brief Pain Inventory). Overall, there were positive relationships between pain coping strategies and pain severity and pain interference, with stronger relationships for people with low SES. SES significantly moderated relationships between select pain coping strategies and pain interference (i.e., reinterpreting symptoms, catastrophizing, praying/hoping) and severity (i.e., reinterpreting symptoms). For example, there was a significant moderating effect of SES on reinterpreting symptoms for pain severity ($b = -0.04$, $p = 0.004$), with a positive relationship between reinterpreting symptoms and pain severity among individuals with low ($b = 0.12$, $SE = 0.04$, $p = 0.001$), but not high ($b = -$

0.03, SE = 0.04, p = 0.48) SES. Overall, some strategies typically deemed “adaptive” (e.g., reinterpreting symptoms) were actually associated with poorer pain outcomes among adults with low SES. To deliver personalized and equitable pain psychology treatment, it is important to recognize that “adaptive” patterns of coping differ based on individual characteristics such as SES.

Examination of Pain Catastrophizing in Sexual and Gender Minorities: Implications for Inclusive Pain Management

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As a result of minority stress (e.g., discrimination), both sexual (SM) and gender minorities (GM) may be more vulnerable to chronic pain conditions, the development of which is associated with pain catastrophizing (PC). PC is a phenomenon where individuals have exaggerated negative mindsets towards pain and is more severe in SGMs. Differences in PC between gender groups are documented. However, literature on differences across sexual orientation groups and the interaction between gender and sexual orientation is limited. This gap prevents nurses from providing a nuanced approach to pain management for SGMs who have worse outcomes traditional pain management programs.A sample (N = 617, age range: 18-65 years) of gender-diverse participants were recruited via social media to complete an online survey. Participants who completed the Pain Catastrophizing Scale were 49.3% heterosexuals, 62.4% cisgender, and 27.9% reported chronic pain. We used a 2 (heterosexual or sexual minority) x 4 (cisgender men, cisgender women, transmasculine, and transfeminine) ANOVA. We found that SM had significantly higher PC than heterosexual individuals, while cisgender women, transmasculine, and transfeminine participants had substantially higher PC than cisgender men. However, no interaction effects were observed.This is the first study to examine sexual orientation and gender effects on PC in tandem. Our findings suggest that SGMs experience greater PC, likely resulting from minority stress, which may increase their likelihood of pain chronification. As such, nurses working with SGMs in the contexts of acute and chronic pain management should consider multimodal interventions addressing physical sensations and psychological processes.

“I’ll Just Take Care of it Myself”: A Qualitative Study of Advanced Cancer Pain Management in Rural Oklahoma

Sara DeForge, Jian Zhao, Ashton Baltazar, Jenson Kaithamattam, Ryan Nipp, Julia McQuoid, Desiree Azizoddin; Dana-Farber Cancer Institute

Adults with advanced cancer who live in rural areas commonly experience obstacles to adequate pain management, resulting in poorly controlled pain. We conducted qualitative interviews to better understand rural Oklahomans’ experiences managing advanced cancer-related pain. We recruited patients(N=11) age>21 years with an incurable solid or hematologic malignancy who resided in rural Oklahoma(RUCA code>4) from the sole NCI-designated cancer center in Oklahoma. Using a critical-realist approach, we conducted one-on-one semi-structured interviews to explore participants’ pain self-management, healthcare utilization, and daily lives.

We transcribed interviews verbatim and analyzed the data using reflexive thematic analysis. Participants were age 62, on average, 73%male, 64%white, and 27%American Indian. Over half(55%) held a high school diploma or less and most(73%) had an annual income<$40,000. Participants indicated that self-reliance and opioid stigma were interwoven with rural cultural identity. Severe pain conflicted with identity-maintaining behaviors (e.g.,"mind over matter") and contributed to pain catastrophizing, resulting in improper opioid dosing. Participants reported repeated miscommunications, logistical issues, and delays related to their healthcare. The perceived impact of these issues was amplified by prolonged commutes to the cancer center, financial difficulties, and opioid regulations. For rural Oklahomans with advanced cancer and pain, intrapersonal, interpersonal, and systemic obstacles combined to produce a feeling of disregard by clinicians and staff, which ultimately impacted engagement with cancer care, pain management strategies, and coping. These findings highlight the importance of providing culturally competent care that includes open acknowledgement of both identity and the structural barriers that rural patients face when seeking cancer pain treatment.

Cardiovascular Measures Are Associated With High Impact Pain In Patients Seeking Treatment For Temporomandibular Joint Disorders

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The autonomic nervous system (ANS) regulates many unconscious physiological processes, including heart and lung function, digestion, and arousal. In its role as modulator of the body's response to environmental and internal stressors, the ANS impacts nociceptive function through a number of mechanisms. Stress and autonomic dysregulation have been identified as potential risk factors for the development of chronic pain conditions such as temporomandibular joint disorders (TMD). In a diverse cohort of 1,049 TMD patients, we investigated associations between self-reported stress (measured using the Perceived Stress Scale, or PSS) and measures of blood pressure and heart rate observed at their first appointment. Patients were grouped into pain impact categories based on two clinical factors. The first divided patients that reported no other pain outside of the orofacial region (n=337) from patients that reported at least one comorbid site of pain (n=712). The second was based on a clustering algorithm using psychological distress and pain sensitization to group patients into Adaptive (A, n=356), Pain Sensitive (PS, n=267), and Global Symptoms (GS, n=281) clusters. We observed significant differences in PSS scores between local-only and comorbid TMD, and the comorbid pain group exhibited higher heart rate and HR/MAP (heart rate over mean arterial pressure) values. Among clusters, the high-impact GS cluster had elevated PSS scores compared to the other two clusters, but the A cluster had lower HR and HR/MAP values than the other two clusters. Mediation analyses among these measures characterize a causal pathway linking stress, ANS reactivity, and high impact pain.

Toward Equity in Chronic Pain Care: Pilot-Testing a Patient Engagement Intervention for Black Patients with Chronic Pain and Depression

Sean Carey, Joanne Daggy, Susan Ofner, Kevin Rand, Marianne Matthias, Adam Hirsh; Indiana University

Despite evidence for their safety and efficacy, non-pharmacological treatments (NPTs) for chronic pain (CP) remain underutilized. Barriers to NPT use include poor patient-provider communication and lack of information; these barriers are exacerbated for both Black patients and patients with comorbid depression. To address these disparities, we conducted the Equity Using Interventions for Pain and Depression (EQUIPD) study to develop and pilot-test an intervention to enhance patient engagement, increase shared decision-making, and reduce pain and pain-related symptoms among Black patients with CP and depression. Patients from a Midwest safety-net health system were randomized to the intervention or wait-list control. The intervention comprised four coaching sessions delivered by phone over three months. These sessions incorporated a Decision Aid to foster shared decision-making about NPTs, and to build skills to enhance patient engagement. All patients (N=30, Mage=60.6 years, 70% female) completed baseline and follow-up measures of pain, depressive symptoms, patient engagement, self-efficacy in physician interactions, and shared decision-making. Because this was a pilot study, we focused on effect sizes in the between-groups analyses of outcomes. At six months, patients in the intervention reported greater patient engagement (Hedge's g=.47, small-to-medium effect), self-efficacy in physician interactions (g=.18, negligible-to-small effect), and shared decision-making (g=.49, small-to-medium effect), and lower pain severity (g=-.41, small-to-medium effect), pain interference (g=-.30, small effect), and depression (g=-.37, small-to-medium effect). These results provide preliminary support for the EQUIPD intervention and informed a fully-powered trial that is currently underway. Funding: R61NR020845.

Using Network Analysis to Understand Pain, Psychological Symptoms, and sSeep Disturbance During Acute Pain Exacerbations Among Groups of Cancer Patients Presenting to Emergency Department with Pain: The Impact of Recent Surgery

Jian Zhao, Kristin Schreiber, Jenson Kaithamattam, Sara DeForge, Peter Chai, Robert Edwards, Hailey Bulls, Desiree Azizoddin; Dana-Farber Cancer Institute

Pain is a common complaint among cancer patients presenting to the emergency department (ED). This study examined relationships among pain and psychological symptoms in patients with cancer and compared relationships between those who had undergone surgery within or beyond 3 months. In this prospective observational cohort, 120 patients who presented to the ED with pain (NRS > 4/10) completed self-report measures on demographics, cancer treatments, pain, medication use, and psychological symptoms (depression, anxiety, catastrophizing, sleep disturbance). Network analysis estimated precision matrices for patients with recent (<3 months, n=49) and distant (>3 months, n=71) surgery, evaluating centrality (direct connections), closeness (network proximity), and betweenness (bridging function). Scores were normalized (0-1), with higher values indicating stronger connections, proximity, or bridging roles. Among patients with recent surgery, helplessness (centrality = 0.85; closeness = 0.85) emerged as the most interconnected symptom, while average pain intensity bridged physical and psychological symptoms (betweenness = 0.44). For patients with distant surgery, pain interference (centrality = 0.86; closeness = 0.86) and average pain severity (centrality = 0.86; closeness = 0.86) were most central. Sleep disturbance exhibited the highest betweenness (0.53), linking symptom clusters. Network analysis highlights dynamic symptom interconnections in post-surgical cancer patients,

with helplessness, pain interference, and sleep disturbance emerging as key targets for intervention, depending on recovery phase. Future studies should adopt longitudinal designs to confirm these observations and explore targeted interventions to improve symptom management and reduce ED visits among cancer patients.

Unemployment And Delayed Medical Care Modify The Relationship Between Single Versus Multi-joint Osteoarthritis And Pain Severity Among Adults In The United States
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Osteoarthritis (OA) is a leading cause of disability and pain; however little is known about whether Social Determinants of Health (SDoH) differ in patients with single versus multi-joint OA (MJOA). We investigated factors related to pain among adults with OA across the United States and whether SDoH modified the relationship between OA group and pain. This cross-sectional analysis utilized data from the All of Us cohort (2018-2023). Single joint and MJOA were determined from electronic health records. Demographics, SDoH, pain severity and daily physical capability were collected from surveys and compared using t-tests, chi-square tests, and multivariable linear regression models. Inverse probability weighting linear models were used to adjust for demographic and socioeconomic differences due to missingness. Of 410,361 participants, 87,400 (21%) had OA (62% female; 62% White; 83% non-Hispanic, 69% >65 years old). Of these, 45% had single joint OA, 43% had MJOA, and the rest were unspecified. Adjusting for other predictors of MJOA, SDoH including unemployment and delayed medical care, are associated with worse pain and this is especially true for patients with MJOA compared to patients with single joint OA. Compared to single joint OA, MJOA patients may be more impacted by unemployment and delayed medical care. Future research should explore the causal pathways between SDoH and MJOA, determining whether these SDoH precede or are exacerbated by the condition and how to best support patients in these contexts.

The Influence of Emotion Regulation Strategies on Subjective Knee Pain in Individuals with Anterior Cruciate Ligament Reconstruction
Francesca Genoese, Matthew Harkey, Shelby Baez; University of Wyoming

Individuals with anterior cruciate ligament reconstruction (ACLR) often experience cognitive and emotional responses to injury that are linked to worse knee-related pain. Although emotion regulation (ER), the process by which individuals monitor, evaluate, and modify their emotions, can influence pain experiences, it is unknown whether specific ER strategies (e.g., cognitive reappraisal and expressive suppression) are associated with knee-related pain after ACLR. This study examined the association between ER strategies and knee pain in individuals with ACLR. We hypothesized that reappraisal tendencies (i.e., reinterpretation of a stimulus) would be associated with less knee pain, while suppression tendencies (i.e., inhibition of behavioral expression) would be associated with more knee pain. Thirty participants (age: M=18.9[SD=2.6] years) with primary, unilateral ACLR (time since surgery [TSS]: M=19.7[SD=15.3] months) were enrolled. ER strategies were assessed with the Emotion Regulation Questionnaire (ERQ) Reappraisal and Suppression subscales, where higher scores reflect individuals' tendency to use

each strategy. Knee pain was measured with the Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain subscale, where higher scores indicate less knee pain. Separate multiple linear regression analyses were conducted to examine associations between each ERQ subscale score with KOOS-Pain scores. When controlling for age and TSS, ERQ-Reappraisal (M=5.18[SD=0.94]) was significantly associated with KOOS-Pain (M=95.28[SD=5.03]) (p=0.01, regression coefficient=2.43), while ERQ-Suppression (M=3.12[SD=0.91]) was not associated with KOOS-Pain (p=0.69, regression coefficient=-0.41). These findings suggest that individuals with ACLR who exhibit cognitive reappraisal tendencies may experience less knee pain. Integrating cognitive reappraisal training strategies throughout ACLR rehabilitation may reduce knee pain in this population.

Patient-generated Values and Goals During a Remotely-delivered Pain Coping Skills Training for People with Chronic Pain Receiving Maintenance Hemodialysis

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For people receiving hemodialysis for kidney failure, chronic pain is prevalent and interferes with patient's values and life goals. Incorporating patients' individual life goals is recommended in guidelines for person-centered care. The objective of this analysis was to classify patient-generated values, value-based goals, and perceived barriers to goal accomplishment during a remotely-delivered Pain Coping Skills Training (PCST) for patients with chronic pain receiving in-center HD. This was a secondary analysis from the HOPE Consortium randomized trial comparing PCST to usual care in patients receiving HD. Qualitative data on patient-generated values, goals, and barriers were identified from audio recordings and notes available from PCST sessions for 225 of the 319 participants assigned to PCST. Two coders conducted qualitative content analysis: they independently categorized each value, goal, and barrier; met to define summary categories/subcategories; confirmed inter-rater reliability; and met for consensus/thematic discussions. A total of 587 values, 709 goals, and 259 barriers were categorized. Value categories (frequency[%]) included Relationships(n=187[32%]), Health(n=150[26%]), Personal Qualities(n=75[13%]), Faith(n=55[9%]), Independence(n=54[9%]), Leisure/hobbies(n=42[7%]), Vocation/education(n=24[4%]). Goal categories included Social/relational(n=197[28%]), Physical Activity(n=175[25%]), Health Behaviors(n=127[18%]), Recreation/hobbies(n=55[8%]), House/yardwork (n=52[7%]), Outings(n=48[7%]), Faith-based activities(n=36[5%]), Profession/education(n=16[2%]). Barrier categories included Physical/medical(n=103[40%]), Mental/emotional(n=68[26%]), Structural/logistical(n=64[25%]), Relational/interpersonal (n=24[9%]). Subcategories are not reported here. A theme was the importance of family such that physical activity/health goals were commonly made in service of family values, not only of health. Many goals required seeking assistance to accomplish, but lack of structural or relational support were commonly perceived barriers. This study provides insight into valued goals of patients with chronic pain receiving HD.

Family Dysfunction, Trauma, Pain, & Substance Use Disorder in Childbearing-Aged Females

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Pain can contribute to substance use disorder (SUD) development. Childbearing-aged females experience more lifetime pain making them vulnerable to SUD. There are indications that psychosocial factors of childhood and/or adult trauma contribute to pain development. Family dysfunction directly influences childhood and adult traumatic consequences in other populations. Consequently, we hypothesize that for childbearing-aged females, the relationship of pain's contribution to SUD development is strengthened by the precursory factors of family dysfunction, childhood trauma, and adult trauma.This nonexperimental correlational study explored relationships between pain, trauma, family dysfunction, and SUD development in a sample of U.S. childbearing-aged females self-reporting chronic pain. The Tobacco, Alcohol, Prescription Medication and Other Substances screen (TAPS-1) was used to sort participants into groups with and without drug misuse. Family-of-Origin Scale (family dysfunction), Adverse childhood events (childhood trauma), Adult Adverse Events (adult trauma), and PROMIS-29 pain intensity and interference subscale scores were used to examine relationships between variables of interest. Regression analysis results indicated a 46% increase in the odds of SUD with 2 unit increases in the Adult Adverse Experiences score, and a 68% increase in the odds of SUD with 2 unit increases in pain intensity scores.Only high ratings for Adult Adverse Experiences were significantly correlated with high pain scores. These results suggest that adult trauma is an area to focus development of trauma-informed interventions in future studies addressing chronic pain and prevention of SUD in this population. NINDS Postdoctoral Training Fellowship (T32NS045549-16A1), and Lila M. Johnson Fund, University of Iowa College of Nursing.

Exploring Quality Of Life In Macromastia: Evaluating Chronic Pain, Mental Health Outcomes, And Insurance Limitations

Gabby Young, Zeinab Mhanna, Lanah Almatroud, Natoisha Cunningham; Michigan State University College of Human Medicine

Exploring Quality Of Life In Macromastia: Evaluating Chronic Pain, Mental Health Outcomes, And Insurance LimitationsGabby Young, Zeinab Mhanna, Lanah Almatroud, and Natoshia Cunningham; Michigan State University College of Human MedicineMacromastia, or excessively enlarged breasts, is a major cause of chronic neck, shoulder, and back pain that has significant negative impacts on overall physical and mental health. Symptomatic macromastia is often intractable to conservative treatments, however, coverage for breast reductions are frequently denied by insurance companies based on outdated criteria. This review explores how macromastia impacts quality of life, including chronic musculoskeletal pain, body image satisfaction, and mental health. Insurance coverage barriers and access disparities are also explored with the goal of guiding healthcare providers toward more inclusive and equitable care. A comprehensive literature search was conducted in PubMed, targeting publications from March 2014 to March 2024. Keywords included "macromastia," "reduction mammaplasty," "breast reduction," "screening," "assessment," "chronic pain," "quality of life," "treatment outcome," and

"satisfaction." Included studies were published in English and focused on breast reductions for macromastia. 86 articles met criteria for inclusion in our analysis. The literature strongly supports reduction mammoplasty for the treatment of symptomatic macromastia, noting postoperative declines in back and neck pain, physical restrictions, and depression in adolescents and adults. Despite its cost-effectiveness and high satisfaction compared to other symptom management methods, insurance coverage for the procedure remains inconsistent and disproportionately affects patients of lower socioeconomic status. These findings aim to inform clinical recommendations for the care and management of macromastia.

Characterizing Access to, and Uptake of, Biofeedback for Chronic Pain
Margaret Rose-McCandlish, Lindsay Flegge, Adam Hirsh; Indiana University Indianapolis

Biofeedback is a longstanding psychophysiological treatment for chronic pain that has seen renewed interest due to the opioid epidemic. In this study, we compared patients who did/not initiate and complete a new six-session biofeedback program for chronic pain. Twenty-six patients have been referred thus far: eight declined treatment, four attended at least one session but did not complete the entire program, two completed the program, six are currently enrolled, and six are on the waitlist. Patients who did not initiate treatment lived twice as far from the clinic (mean = 38.2 vs. 16.8 miles; Wilcoxon r = -0.2) and were on the biofeedback waitlist longer (mean = 245.9 vs. 138.4 days; Wilcoxon r = -0.3) than those who initiated or are awaiting treatment. Of patients who completed at least one session, those who discontinued were older (56.8 vs. 45.3 years; Wilcoxon r = -0.4) and had a longer waitlist time (196.7 vs. 113.4 days; Wilcoxon r = -0.3) than those who completed or are currently enrolled in the program. Neither referral source, disability status, nor employment status showed notable differences between patients who declined treatment vs. those who initiated or are awaiting treatment, or between patients who discontinued the program vs. those who completed or are currently enrolled in the program. These findings suggest that longer wait times, greater travel distance, and older age are key barriers to participation in the program, highlighting the need to address demographic and logistical challenges to ensure equitable access to biofeedback for chronic pain.

Exploring Changes in Perceived Injustice Following a Brief Psychological Intervention in Subacute and Chronic Low Back Pain After Work Injury in the Context of Physical Therapy
Naz Yagmur Alpdogan, Junie Carrière, Marie-France Coutu; Université de Sherbrooke

This study examined whether changes in perceived injustice are associated with changes in pain catastrophizing among adults with occupational low back pain undergoing physical therapy and a brief psychological intervention. Secondary analyses from a larger project used data from 63 participants (42 with subacute pain, 21 with chronic pain) enrolled in physical therapy and completing a two-hour Empowered Relief intervention. Measures included the Injustice Experience Questionnaire, Pain Catastrophizing Scale, and PROMIS Pain Intensity, Anxiety, and Depression questionnaires, collected at baseline and 4-week follow-up. Statistical analyses included paired t-tests, correlation, and regression analyses. Participants with subacute pain

experienced a 60.3% reduction in perceived injustice ($p < 0.001$, Cohen's $d = 1.81$) and a 71.6% decrease in pain catastrophizing ($p < 0.001$, Cohen's $d = 2.44$). Regression analyses identified changes in pain catastrophizing as the strongest predictor of changes in perceived injustice ($\beta = 0.652$, $p < 0.001$), with the rumination subscale particularly impactful. Chronic pain participants showed a smaller, non-significant reduction in perceived injustice (16.8%, $p = 0.075$) but a significant 43.56% decrease in pain catastrophizing ($p < 0.001$, Cohen's $d = 2.34$). Among subacute participants, reductions in the blame ($\beta = 0.160$, $p = 0.003$) and severity ($\beta = 0.616$, $p = 0.002$) subscales of perceived injustice were significantly associated with rumination reductions—an effect not observed in chronic participants. These findings suggest that perceived injustice is associated with pain catastrophizing only in the subacute pain phase. Stage-specific approaches appear important, emphasizing early screening and intervention to improve recovery outcomes.

Psychometric Evaluation of the Future Self Questionnaire in a Sample of Individuals with Chronic Pain

Tyler D. Barrett, Rhonda M. Williams, Mark P. Jensen; University of Washington

The concept of future self can be defined as an individual's expected view of themselves in a future context. Research has shown that how individuals perceive their future selves is associated with their current function, and might predict treatment outcomes. However, previous approaches for measuring future self perceptions are complex and time-consuming. The Future Self Questionnaire (Future-SQ) is a 15-item instrument developed to measure an individual's view of their future self. The purpose of this study was to identify the component structure of the Future-SQ and evaluate its validity and reliability in a sample of individuals with chronic pain. 150 participants in an ongoing clinical trial comparing three psychological pain interventions completed the Future-SQ and a set of criterion validity variables at baseline. We performed a principal component analysis and examined the resulting eigenvalues, scree plot, and pattern matrix of the Future-SQ items. The results indicated the items measure 2 components, which we labeled Health and Fitness and Self-Management. The Cronbach's alphas of the two subscales and the total scale were .77, .93, and .92, respectively, suggesting acceptable to excellent reliability. Correlational analyses with validity criterion variables indicated strong associations with convergent validity and weak associations with discriminant validity measures. The findings support the reliability and validity of the Future-SQ for use in individuals with chronic pain, suggesting that the measure may be used in research to evaluate the effects of treatments on future self perceptions and subsequent effects of these changes on outcomes. NIH/NCCIH: R01AT011012.

Integrated Behavioral Health Services for Individuals with Chronic Musculoskeletal Pain: Perspectives from Rheumatology Healthcare Professionals

Shannon Teaw, Jessica Link-Malcolm, Dorothy Patterson, Michelle Ghebranious, Una Makris; University of Texas Southwestern Medical Center

Chronic musculoskeletal (MSK) pain is prevalent and debilitating in individuals with rheumatic diseases (RD); the pain may be due to autoimmune inflammatory conditions and/ or underlying

osteoarthritis or fibromyalgia. Behavioral Health (BH) interventions, such as exercise, cognitive behavioral therapy, and stress management, have been effective in addressing MSK pain. Integrating BH into rheumatology clinics may help manage MSK pain and associated symptoms, however, few effective models exist. Optimal integration of BH services depends on input from stakeholders, including rheumatology healthcare professionals (HCP) during the development of the BH program. The purpose of this study is to explore rheumatology HCP perspectives toward integrating BH services in rheumatology for MSK pain. Physicians and nurse practitioners completed surveys and participated in semi-structured interviews to share their perspectives. Rapid Qualitative Analysis was used to identify thematic domains and illustrative quotes. Twelve HCPs participated in the study. All HCPs recognized the importance of BH, particularly physical activity (N=7) and mental health (N=5), in MSK pain experiences. They reported limited time and expertise to address BH in clinics, preferring co-located, same-day BH services. Barriers included systemic issues (inefficient workflows, limited funding/space), HCP challenges (time constraints, lack of BH training), BH specialist limitations (referral overload), and patient-related obstacles (inconvenience, lack of motivation, stigma). These findings demonstrate HCPs' awareness of the importance of BH in MSK pain management and the barriers to service integration. These insights inform the development of a pilot BH program in rheumatology settings and may extend to other specialties managing chronic pain.

Mindfulness-Based Cognitive Therapy for Pain and Suicide: A Feasibility and Acceptability Study

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Pain is associated with increased suicide risk, yet few interventions address both. The purpose of this study was to assess the feasibility and acceptability of mindfulness-based cognitive therapy for pain and suicide (MBCT-P/S) among Veterans with chronic pain at risk of suicide. Participants (n = 76) were recruited to participate in a telehealth-based randomized clinical trial from the Syracuse VAMC and VA Finger Lakes through case finding procedures using the electronic health record. Participants received either the 10-session MBCT-P/S or Health Education; both included treatment-as-usual. Measures assessing suicide risk, pain interference and potential mechanisms were completed at baseline, and 1-month, 3-month, and 6-month post-treatment. Acceptability was evaluated using rating scales indicating levels of agreement about statements on the intervention (1=strongly disagree to 5=strongly agree). Target enrollment was met ~9 months earlier than anticipated with suicide risk, pain interference, and other indicators reflecting a clinically severe sample. Although follow-up data collection is ongoing, retention at the 3- and 6-month follow-up assessments are above 80%. Approximately 60% of sample across both conditions attended at least half of the sessions. Participants randomized to MBCT-P/S consistently reported high treatment acceptability (e.g., I benefitted from this intervention – M=4.32; SD=0.95; This intervention was an acceptable intervention for suicidal thoughts and pain – M=4.05; SD=0.78). This study has demonstrated promising feasibility and acceptability of a randomized clinical trial of MBCT-S/P among Veterans with chronic pain at risk for suicide. We will continue to evaluate retention and are currently evaluating of therapist fidelity to the intervention. R34AT0110004.

Mind The Gap: Success Criteria Versus Treatment Expectations Among Patients Referred To A Pain Psychology Clinic

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While psychological interventions effectively reduce chronic pain symptom severity, less is known about patients' expectations and definitions of success. This information is particularly important for psychological care, where treatment engagement and aligned expectations influence outcomes. To address this gap, we investigated patient-reported expectations, success criteria, and outcome priorities among 525 adults seen in a pain psychology clinic. Using the Patient-Centered Outcomes Questionnaire, we assessed symptom burden, expectations for treatment, and definitions of success across four domains using a 1-10 Likert Scale: pain, fatigue, emotional distress, and interference with daily activities. Analyses revealed considerable symptom burden at intake (mean ± SD): pain (6.27 ± 2.25), interference with daily activities (6.46 ± 2.55), fatigue (5.79 ± 2.62), and emotional distress (5.19 ± 2.74). Patients prioritized improvements in pain intensity (8.49 ± 2.53) and interference (8.10 ± 2.69) over emotional distress (7.15 ± 3.28) and fatigue (7.05 ± 3.18). Expected % reduction in symptom burden was consistently lower than patients' criteria for successful symptom reduction across domains: pain (expected: 47.0% vs. success: 51.6%, $p<.001$), fatigue (expected: 46.3% vs. success: 50.6%, $p=.001$), and interference (expected: 51.6% vs. success: 58.1%, $p<.001$), with a similar trend for emotional distress (expected: 46.7% vs. success: 49.5%, $p=.067$). This gap between patients' definitions of treatment success and their expectations for improvement highlights a potential area for addressing expectations in treatment planning. Future analyses will identify psychosocial predictors of treatment expectations, providing a foundation for developing more personalized approaches to psychological pain interventions.

The Link Between Childhood Maltreatment and Later Pain Perception: The Role of Memory Processes and Complex Posttraumatic Stress Symptoms

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Findings reveal that childhood maltreatment (CM) is implicated in alterations in pain perception and a higher risk of chronic pain. However, the underlying mechanisms, or how these alterations are developed are yet to be uncovered. This study was conducted to test the role of unique trauma-related memory processes and complex posttraumatic stress (CPTSD) symptoms for pain perception following CM. A community sample of 232 young adults completed the cold pressor pain task, assessing pain threshold, pain tolerance, and perceived pain intensity of suprathreshold stimuli, as well as self-report questionnaires. Traumatic memory mediated the associations between CM and all CPTSD symptom clusters. Mixed findings were found for the link between CPTSD symptoms clusters and pain perception, with avoidance symptoms and dysfunctional self-organization symptoms implicated in lower pain thresholds ($b<-.19$; $p<.01$). Hyperarousal symptoms were implicated in a higher pain threshold ($b=.61$; $p<.01$). Intrusion symptoms were associated with a higher pain tolerance ($b=1.33$; $p<.05$), while hyperarousal symptoms were implicated in reduced pain tolerance ($b=-.70$; $p<.01$). Indirect paths linking CM and pain perception indices support the above associations. The findings demonstrate a distorted pain

perception following CM, potentially originating in unique traumatic memory processes, and woven in complex patterns of associations with CPTSD symptoms.

Multivariate Sentiment Analysis Of Social Media Posts About Low Back Pain
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Low back pain (LBP) is the world's leading cause of disability, affecting 70-85% of the population, with no identifiable cause in most patients. LBP is a complicated biopsychosocial disease, and individuals use varying coping strategies in response to their unique personal experience with LBP. We propose that understanding, and quantifying, how individuals communicate their LBP can identify coping mechanisms and direct treatment strategies. Towards quantifying how individuals communicate their LBP, in this study, we evaluated posts about back pain from the social media platform Reddit (subreddit: r/backpain, N=21,858) using a modified version of the natural language processing tool Sentiment Analysis and Social Cognition Engine (SEANCE). SEANCE includes 254 core indices and 20 component indices for sentiment analysis. We cleaned data by removing advertisements and posts without an account of a personal experience with back pain (n=4,029). After SEANCE processing, posts with insufficient data (>20% zero values or <80% index coverage) were excluded (n=6,668). The final dataset included N=11,161 posts and 147 sentiment indices. To determine the most prominent sentiments featured in the dataset, a principal component analysis was performed, revealing 73 meaningful dimensions of communication (90% variance). Unsupervised learning revealed 55 clusters with distinct communication sentiments. Posts were 8.6% positive, 13.3% negative, and 78.1% neutral in sentiment, while sadness, fear, trust, and anticipation were the predominant emotions in LBP posts. These results demonstrate the feasibility of quantifying communication sentiments in social media posts about LBP. Future work will determine correlates to communication sentiment and how treatment outcomes vary by sentiment.

Characterizing Daily Experiences of Pain, Opioid Use, and Mood in Patients with Advanced Cancer Pain Using Ecological Momentary Assessment Data
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Pain is a significant, debilitating symptom for many with advanced cancer. This study assessed relationships between pain, opioid use, mood, sleep, and catastrophizing using Ecological Momentary Assessment (EMA) data collected daily for 28 days from 26 participants with advanced cancer and chronic pain (NRS >4). Daily pain intensity(best/worst/average/current), opioid use, mood (negative and positive affect), sleep quality, and pain interference were rated using an mHealth app in the context of feasibility testing of a pain intervention (STAMP+CBT). Multilevel regression models accounted for within- and between-person associations between pain and other symptoms. Baseline pain catastrophizing and day-to-day pain variability were evaluated as moderators of symptom burden. In distinct models, higher overall mean pain intensity was significantly associated with lower opioid effectiveness, worse pain interference, negative mood, and sleep disturbance($p<0.05$). Worst daily pain was associated with increased pain interference ($\beta=0.81$, $p<0.001$) and increased daily opioid use ($\beta=0.23$, $p<0.001$). High daily

catastrophizing was associated with increased opioid use (β=2.04, p=0.048), sleep disturbance (β=0.71, p=0.013), and negative mood (β=0.07, p=0.030). The association of daily pain with negative affect was moderated by catastrophizing. For individuals with high catastrophizing, pain was more strongly associated with sleep disturbance (β=0.158, p=0.015), and more strongly inversely associated with positive affect (β=-0.195, p=0.004), compared to those with low catastrophizing. These findings highlight the insights that EMA can provide regarding the dynamic interplay between pain, mood, sleep, and opioid use for patients with advanced cancer pain, which may be used to personalize in-the-moment interventions for cancer pain management.

Positive Childhood Experiences as a Protective Factor Against Pain and Functional Impairment: The Moderating Role of Adverse Childhood Experiences
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While Adverse Childhood Experiences (ACEs) and other risk factors may worsen health, less is known about how resilience factors such as Positive Childhood Experiences (PCEs) can buffer against adverse health outcomes. The impact of resilience and risk factors should be considered within a balanced context. This study examined whether PCEs influenced pain severity, pain interference, and physical function among 73 individuals undergoing lumbar spine surgery (M age = 63.18, 50% women), whether this relationship was mediated by pain catastrophizing, sleep disturbance, fatigue, and satisfaction with social roles, and whether these effects were moderated by exposure to ACEs. PROCESS Model 7 was utilized to test moderated mediations for each health outcome. Results indicated that PCEs were associated with lower pain severity, and that this effect was mediated through lower pain catastrophizing, lower sleep disturbance, lower fatigue, and higher satisfaction with social roles, but only at low to moderate (2 or fewer) ACEs levels. At high ACEs levels (3 or more), these mediating effects were not present. Similar moderated mediation effects were observed for pain interference. For physical function, significant moderated mediation effects were found for sleep, fatigue, and social role satisfaction, but not for pain catastrophizing. These findings suggest that PCEs may mitigate adverse physical health outcomes, but their protective effects may be constrained to individuals without significant ACEs. It is important to understand how resilience factors like PCEs interact with ACEs and other risk factors, as early-life experiences shape health trajectories and can guide trauma-informed strategies for surgical care.

Socioeconomic Factors Predict Low Back Pain But Not Lumbar Disc Health: Data From The UK Biobank Image Dataset
Mary Bucklin, Ashrith Alavilli, Kastriot Kamberi, Rana Ahmad, Scott Simmons, John Martin; Rush University

Low back pain (LBP) is a disease with biological, psychological, and social components and the interaction of these components is poorly understood. In previous work, we screened hundreds of variables related to musculoskeletal health and identified that income and education were the

strongest predictors of LBP severity and chronicity. However, we could not evaluate anatomical factors like lumbar disc health, which is frequently implicated as a driver of LBP. Here, we evaluated the hypothesis that low socioeconomic status (SES) accelerates lumbar disc disease and LBP. We utilized deep learning to automate the analysis of dual x-ray absorptiometry (DEXA) scans of the lumbar spine from the UK Biobank imaging dataset (N=10,440) to enable a large-scale assessment of lumbar disc health and SES. An existing deep learning model (DeepLab) was repurposed to receive a DEXA scan as input and output segmented lumbar vertebral bodies (train IoU = 0.98, test IoU =.93). Following segmentation, we calculated disc height and disc wedge angle. We used regression models to determine the relationship between LBP and income/multiple deprivation index (MDI) and between disc height/wedge angle and income/MDI. There were significant relationships between income and pain as well as MDI and pain, but no relationship between income or MDI and disc height or disc wedge angle. We conclude that lumbar disc health is not a factor in the LBP phenotype related to SES. Funding: NIH (R00AR077685, T32AR073157, 5TL1TR002388), Stryker/ORS Women's Fellowship.

Kinesiophobia is Associated with Pain Intensity and Interference at 3, 6, and 12 Months Following Discharge from a Level-I Trauma Center

Sriram Koneru, Saara Sherali, Kevin Raleigh, Hope Owens, Phylicia Taylor, John Sturgeon, Megan Reynolds, Kenleigh McMinn, Michael Foreman, Ann Marie Warren, Evan McShan, Zina Trost; Texas A&M University

Kinesiophobia is the fear of movement or physical activity driven by concerns about reinjury and pain. The Tampa Scale of Kinesiophobia (TSK) is an established measure for identifying pain-related fear and reinjury from movement. Previous research suggests that the TSK is predictive of pain and pain interference in populations with musculoskeletal pain. Less is known about the impact of kinesiophobia following major physical trauma. The current study examined the role of kinesiophobia at three time points following hospitalization at a Level-I Trauma Center. Phone surveys were administered to trauma patients who completed the TSK and additional measures at 3, 6, and 12 months following initial hospitalization (each time point comprised a different patient cohort). Correlations and multiple regression analyses were conducted to examine the associations between kinesiophobia and a) pain intensity, b) descriptive pain ratings, and c) pain interference at each time point. TSK scores were associated with greater pain intensity ($r = .51$-$.60$), descriptive pain ratings ($r = .40$-$.53$), pain interference ($r = .47$-$.60$), and depression scores ($r = .56$-$.59$) across all time points (all p's $< .001$). In hierarchical regression analyses, TSK scores significantly accounted for variance in pain intensity, descriptive pain ratings, and interference outcomes above and beyond demographic variables, severity of injury, and depression across all timepoints. These findings underscore the importance of addressing kinesiophobia in trauma settings to improve post-traumatic outcomes and recovery. Support for the study was provided by the Stanley Seeger Surgical Endowment Funds of the Baylor Health Care System.

Adverse Childhood Experiences and Migraine in Adulthood

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Migraine ranks among the foremost causes of disability worldwide, leading to immense personal suffering and high economic cost. A rarely explored factor, potentially contributing to increased migraine burden, is adverse experiences during childhood. Indeed, emerging research suggests that individuals who experience more Adverse Childhood Experiences (ACEs) are at increased risk for both physical and mental health issues, including a higher likelihood of developing migraine. However, it remains unclear whether and how ACEs contribute to worse migraine outcomes such as attack frequency, intensity, and disability. In this study, we sought to elucidate whether more ACEs are associated with substantial psychological symptoms, which ultimately increase migraine frequency, intensity, and disability. This study was conducted online via REDCap and utilized several validated questionnaires, including the Migraine Disability Assessment Questionnaire, the ACEs Questionnaire, the Patient Health Questionnaire-9, and the General Anxiety Disorder-7 Scale. The ACEs Questionnaire is ten questions, which were broken into three groups: no adversity (score of 0), low adversity (score of 1-3), and high adversity (score of 4 or more). Preliminary data suggest a dose-dependent relationship between childhood adversity and migraine disability emerged, with individuals reporting four or more ACEs exhibiting greater migraine-related disability and elevated psychological symptoms. However, ACEs did not appear to significantly impact the intensity of migraine episodes. In conclusion, these findings highlight the impact of ACEs on migraine-related disability and psychological symptoms, underscoring the need for further research into the downstream effects of childhood adversity on migraine onset and prognosis.

Validating the Social Vigilance Questionnaire in a Multi-Ethnic Sample of Individuals with Chronic Low Back Pain

Emma Tillery, Hope Owens, Kevin Raleigh, Phylicia Taylor, Adam Guck, John Sturgeon, Zina Trost; Texas A&M University

The Social Vigilance Questionnaire (SVQ) was designed to quantify the frequency of vigilant cognitions in social contexts. The questionnaire identifies how often one experiences 10 different thoughts in social situations, with items clustered into factors reflecting ‘vigilance for self’, ‘vigilance for others’ reactions to self’, and for ‘vigilance for social threats.’ Previous research has consistently highlighted the central role of attentional processes (towards personal pain) in pain-related outcomes. However, an individual’s attentional orientation toward their social environment has yet to be examined in the context of pain experience. Adults (n=148) with chronic low back pain and endorsing significant pain interference completed self-report measures, including the SVQ. A confirmatory factor analysis specifying the 3-factor structure of the SVQ was conducted using Mplus version 6.12. The model fit was acceptable according to 4 of 5 indices (CFI = .957, TLI = .939, SRMR = .044) but indicated poor fit according to chi-square test of model fit ($\chi 2(32) = 60.8$, $p < .001$). Internal consistency of the subscales (Cronbach’s alphas ranging from .72 to .84) and the total scale (alpha = .89) were acceptable to good. The model fit was generally acceptable but fell below established standards for good model fit for some fit indices. This pattern of results may be due to differential item fit according to clinical or demographic factors, such as racial or ethnic status. These factors warrant further examination in larger samples within future studies examining social vigilance.

The Lived Experience of Driving with Pain

Misha Shah, Sara Hiller, Jackson Gutierrez, Sriram Koneru, Hope Owens, Kevin Raleigh, Phylicia Taylor, Nina Attridge, David Moore, Despina Stavrinos, Zina Trost; Texas A&M University

Chronic low back pain (CLBP) is a prevalent condition that affects individuals' routine behaviors, including driving. Previous studies have examined the effects of chronic pain on driving, such as impaired mobility and reaction times. This study aimed to identify the qualitative themes related to driving with CLBP as well as common methods of coping with pain in this context. Participants who endorsed low back pain for at least half of the days in a three-month period were asked to respond to two prompts about their driving experience. The prompts administered were: "Please let us know how pain affects your driving or experiences on the road," (n=298) and "Please let us know what types of things you do to cope with pain while driving," (n=299). An inductive thematic analysis of the responses was conducted through a large language model to identify common themes. Analyses revealed responses fitting into two categories. Category 1, Experience of Driving, included the themes (1) Irritation and Impatience, (2) Difficulty Focusing, (3) Physical Discomfort, and (4) Road Rage. Category 2, Coping Strategies, included the themes (1) Driving Avoidance, (2) Physical Adjustments, (3) Medication, (4) Behavioral Strategies, and (5) Pain Management via Lifestyle Changes. This analysis highlights several research targets within 'Experience of Driving' and 'Coping Strategies' with potential to improve the driving experience for individuals with CLBP. Further research should examine methods for addressing the emotional aspects of driving with CLBP and the effectiveness of identified coping strategies.

Evaluating the Psychometric Properties of the Pain Coping Response Measure in a Diverse Young Adult Sample

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In the U.S., approximately 20.4% of adults suffer from chronic pain. Pain coping (i.e., cognitive and behavioral strategies used to manage pain) has been identified as a predictor for successful pain management. Existing pain coping measures have primarily been developed for use within clinical pain populations. There is a notable gap in pain coping research for non-clinical young adult samples, presumably, because this group is not at immediate risk for severe chronic pain. However, from a preventive perspective, young adults are at a unique point in their development wherein health habits are being established and carried into adulthood. This analysis sought to evaluate the psychometric properties of the Pain Coping Response Measure (PCRM; Litt et al., 2009) within a young adult sample. Cross-sectional data was collected on 335 young adults (Hispanic/Latino = 78.5%) enrolled at a large Hispanic-Serving Institution in Southern California. The internal consistency reliability for all multi-item subscales was unacceptable ($\alpha s \leq .50$). Factors derived from the exploratory factor analyses did not match the subscales proposed by Litt et al. (2009). For comprehensiveness, convergent validity using the structure of the original subscales was conducted, however, most of the subscales proposed by Litt et al. (2009) were not correlated with the Ways of Coping Checklist-Revised (WCCLR; Vitaliano et al., 1985) subscales. The psychometric analyses suggest that the PCRM subscales were not reliable or

factorially valid in the current sample, however, well-performing individual items should be considered for future psychometric studies.

Pain Catastrophizing and Central Sensitization, Not Pain Severity, Predicts Treatment Engagement Among Patients on Opioid Therapy for Pain

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Given the known risks of long-term opioid therapy (LTOT), it is important to understand what predicts engagement in other non-opioid treatments for chronic pain (CP). We aimed to examine the relative impact of psychological (pain catastrophizing) and psychophysiological (central sensitization) factors, above and beyond physical factors (pain severity), on the number of non-opioid treatments sought by adults with CP on LTOT. Recruited participants included adults (N=157) with a CP condition actively prescribed an opioid. A hierarchical multivariate linear regression was calculated with predictors including the Brief Pain Inventory (BPI), the Central Sensitization Inventory (CSI), and the Pain Catastrophizing Scale (PCS). Our outcome included non-opioid reported treatments utilized for CP. The first model predicting treatment utilization from pain severity was nonsignificant [$F(1, 155)=.003$, $p = .959$]. The second model was significant after adding PCS and CSI [$F(3, 153) = 9.02$, $R2 = .15$, $p < .001$]. Higher central sensitization ($B = .38$, $p < .001$) and lower pain catastrophizing ($B = -.41$, $p < .001$) predicted higher utilization of other treatments, while pain severity was nonsignificant ($p > .05$). Among patients with CP on opioids, higher central sensitization scores and lower pain catastrophizing predicted more engagement in alternative pain treatments, while pain severity did not. Greater centralized pain could indicate an unclear path for treatment, contributing to more treatment seeking. It is unclear if lower pain catastrophizing is associated with higher use of treatments due to anxiety-reducing effects following engagement, or if higher pain catastrophizing is a barrier to treatment-seeking.

Neighborhood Context and Race Shape the Relationship Between Cognition and Pain

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While socioeconomic disparities in pain are well-documented, the interplay between cognitive function, neighborhood context, and pain—particularly across racial groups—remains poorly understood. This study examined whether neighborhood disadvantage moderates the relationship between cognitive function and movement-evoked pain (MEP) and assessed racial differences. 268 adults with knee osteoarthritis (KOA; age = 61.22 ± 8.86 years; 50.4% non-Hispanic Black (NHB), 49.6% non-Hispanic White (NHW); 67.8% female) completed the Montreal Cognitive Assessment (MoCA) and pain questionnaires. Neighborhood disadvantage was estimated using the state-level area deprivation index (ADI; 1 = least deprived, 10 = most deprived). Average ADI was 5.95 (SD = 3.11), with values of 6.79 (SD = 3.00) for NHB and 5.10 (SD = 3.00) for NHW participants. Bivariate associations were observed for MoCA and MEP ($r = -0.28$, $p < 0.001$**), MoCA and ADI ($r = -0.28$, $p < 0.001$**), and MEP and ADI ($r = 0.21$, $p < 0.001$**).

Overall, ADI did not moderate the MoCA-MEP relationship (B = -0.08, p = 0.57). However, race-stratified analyses, probed at high (+1 SD), average (M), and low (-1 SD) ADI level, revealed moderation effects. Among NHW participants, lower cognitive function predicted greater MEP in highly deprived neighborhoods (B = -2.33, p = 0.01*). For NHB participants, ADI did not moderate the MoCA-MEP relationship (B = 0.19, p = 0.38). Well-resourced neighborhoods may buffer cognitive vulnerability for NHW adults. The absence of this effect for NHB adults highlights systemic inequities. Cognitive health and neighborhood context are key intervention points for KOA pain.

Valproate Attenuates Orofacial and Somatic Hyperalgesia Induced by Maternal Separation Through Inhibiting IL-6 in the Medial Prefrontal Cortex and Spinal Cord.
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Sodium valproate (VPA), as a histone deacetylase (HDAC) inhibitor, has been shown to have analgesic effects and may be involved in analgesia through anti-inflammatory mechanisms. However, little is known about the involvement of VPA in the treatment of comorbid chronic pain conditions such as fibromyalgia syndrome (FMS) and temporomandibular disorder (TMD). Here the rat pups were subjected to 3 hours of daily maternal separation stress from postnatal day 1 (PND1) to PND21 to simulate childhood stress-induced TMD and FMS comorbidity at different age stages. Fresh tissues from the medial prefrontal cortex (mPFC) and L4-L5 spinal dorsal horn were collected on PND22, PND35, and PND55 for Western blot. We found that maternal separation stress induced orofacial and somatic hyperalgesia in both male and female adolescent and adult rats, along with increased protein expression of IL-6 in the mPFC and the dorsal horn of L4-L5 spinal cord. Intraperitoneal injection of VPA reversed the stress-induced orofacial and somatic hyperalgesia as well as the increased expression of IL-6 in rats without gender differences. Conversely, microinjection of recombinant IL-6 protein into the mPFC region or intrathecal injection of recombinant IL-6 protein reversed the analgesic effect of VPA. These results suggest that VPA may exert its therapeutic effects on stress related TMD and FMS comorbidity by inhibiting IL-6 release in the brain and spinal cord. Funding: National Natural Science Foundation of China (81971049 and 81671097).

Delayed Diagnosis in Fibromyalgia: A Mixed Method to Investigate the Experience and Impact of Diagnosis on Physical and Mental Wellbeing
Kabir Mayana Isah; University of Hertfordshire

Fibromyalgia is a chronic, widespread pain condition accompanied by other debilitating symptoms. There is a paucity of data on the impact of time of diagnosis on physical and psychosocial symptoms. This study aims to explore the experiences of individuals with fibromyalgia regarding their diagnostic journey and the subsequent effects on their well-being. A convergent mixed methods approach was employed, combining survey data with semi-structured interviews. The survey included responses from 248 patients diagnosed with fibromyalgia recruited from UK fibromyalgia organisations. Additionally, semi-structured interviews were concurrently conducted with a selection of 14 participants. The survey investigated the duration

from symptom onset to diagnosis and its relationship with pain and psychological symptoms. The interviews provided a deeper understanding into the personal and contextual impact of delayed diagnosis. The survey revealed that over 60% of participants were diagnosed more than five years after symptom onset, with a significant positive relationship between delayed diagnosis with mood and depression ($P < .05$). Qualitative data from interviews corroborated these findings, highlighting the emotional and psychological trauma experienced by patients and their families due to the prolonged diagnosis process. This study underscores the critical need for timely diagnosis of fibromyalgia to mitigate the adverse effects on patients' mental wellbeing to improve the quality of life for individuals with fibromyalgia and their families.

Cost-Effectiveness of a Tailored Pain Self-Management Intervention Among People with HIV and Chronic Pain

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Background: Pain self-management (PSM) interventions are low risk, effective interventions for chronic pain that have high potential for scalability. Economic evaluations are a key component to assessing scalability. We evaluated the cost-effectiveness of a tailored PSM (STOMP) as compared to enhanced usual care (EUC) among people with HIV (PWH) and chronic pain.Setting and Methods: Data are from a randomized controlled trial of STOMP (N = 278). From a healthcare perspective, a Markov decision analysis model over a 12-month time horizon was used. Participants were recruited from two academic medical centers within the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. STOMP involves six individual sessions and six peer-led group sessions. The EUC control group received the STOMP treatment manual. The primary outcome was the incremental cost-effectiveness ratio, defined as US dollars per quality-adjusted life-year (QALY) gained derived from trial-based Medical Outcomes Study Short-Form 12 (SF-12) data. Sensitivity analyses examined the effects of parameters varied individually and collectively on model results.Results: Participants were middle-aged (M=53.5, SD=10), male (53%), and Black/African American (81%). Model calculation of effectiveness over the 12-month time horizon resulted in 0.570 QALYs for EUC and 0.603 QALYs for the STOMP intervention, or 0.033 QALYs gained by STOMP compared to EUC. In probabilistic sensitivity analyses that varied all parameters simultaneously, the STOMP intervention was favored in 98.0% of 10,000 model iterations at a $100,000/QALY threshold.Conclusions: STOMP is highly cost-effective and a promising scalable PSM intervention for PWH and chronic pain.Trial Registration: #NCT03692611.

Sex Differences in Pain and Analgesia

Female-specific Long Non-coding RNA Xist-E3 Ligase Interactions Regulate Acute Inflammatory Pain In Females

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Epidemiological studies demonstrate a greater incidence of acute inflammation in men and chronic inflammation and pain in women. While mechanisms are not fully understood, the female immune system is generally recognized to have stronger antigenic responses, partly attributed to aberrant gene regulation of the X chromosome. Recently, expression of X-inactive specific transcript (XIST), a female-specific long noncoding RNA which regulates X-chromosome inactivation in females, has been recognized to play a key role in autoimmune and autoinflammatory disorders. However, little is known on how XIST may contribute to disparities in acute inflammation. Our in vitro studies show lipopolysaccharide-induced acute inflammation increases Xist in the cytoplasm of female mouse J774A.1 macrophage cells. Cytoplasmic Xist colocalized with the p65 subunit of NF-κB, delaying NF-κB nuclear migration suggesting a novel temporal and spatial mechanism by which Xist suppresses acute inflammation in female cells. Supporting this, male cells transfected with 5' XIST reduced NF-κB translocation and IL-6 translation. RNA antisense purification with mass spectrometry, identified an E3 ubiquitin-protein ligase (RNF) that interacts with Xist in the cytoplasm, exclusively under acute inflammation. Interestingly, knock-down of either Xist or RNF results in reciprocal downregulation of the other gene in female cells only. RNF knockdown in mouse models of inflammatory pain increases pain duration in females. Studies examining sex specific ubiquitination targets of RNF in vivo in the dorsal root ganglion and in vitro are ongoing. These studies identify a novel function for XIST beyond X-inactivation, providing insight on sex specific targets underlying acute inflammation and pain.

Sex Differences in Endocannabinoid Levels and Associations with Pain Risk Factors in Adolescents

Julia Evanski, Chelsea Kaplan, Steven Harte; University of Michigan Medical School

The endocannabinoid (eCB) system is integral to pain perception and may have antinociceptive effects. This study is the first to examine sex differences in eCB levels, and their associations with pain and risk factors that may contribute to the development or exacerbation of pain symptoms, such as sleep disturbances. Data were analyzed from the Adolescent Brain Cognitive Development Study®, which included a substudy to measure circulating blood eCB concentrations in a subset of participants (n=403, mean age=12.56±1.05 years, 46.4% female). Covariates included age, race and ethnicity, puberty, sex, BMI, fasting state, and recent exercise. Pain was assessed on day of the blood draw (0-10 scale) and sleep disturbances were measured by the number of nighttime awakenings. Five eCB and eCB-like molecules were examined: anandamide (AEA), 2-arachidonoylglycerol (2-AG), palmitoylethanolamide (PEA), oleoylethanolamide (OEA), and 2-oleoylglycerol (2-OG). There was a significant sex difference in 2-AG concentrations (β=-5.36, CI[-8.53-2.18], p-adj=0.005), with female youth having lower concentrations than males. Because of this sex difference, all other analyses were sex stratified. There was no association between pain on the day of the blood draw and eCB concentrations in either sex. Male youth alone exhibited a positive correlation between nighttime awakenings and concentrations of AEA (β=0.62, CI[0.26-0.99], p=0.001) and OEA (β=0.14, CI[0.065-0.21], p<0.001). These findings suggest there may be sex-specific relationships with the eCB system and risk factors for pain. Future analyses will leverage longitudinal eCB measurements and examine how changes in eCB may relate to pain and sleep problems during adolescence.

Chemotherapy Regimens Differentially Modulate CD4+ T cells and Nerve Loss in Peripheral Tissue in Chemotherapy-Induced Peripheral Neuropathy
Kenyah Ferreira, Riley Cott, Diana Goode; University of New England

Chemotherapy is effective at killing cancer cells, but its non-specific nature can damage peripheral sensory neurons resulting in the development of chemotherapy-induced peripheral neuropathy (CIPN). As there is no effective treatment to prevent or manage the painful symptoms, chemotherapy doses are often reduced, delayed, or discontinued. However, it is unclear the extent the change in dose impacts the type of CD4+ T cells in the dorsal root ganglion (DRG) and peripheral skin, and how this might modulate peripheral nerve loss/regeneration. In this study, male and female mice were administered PTX at 6 mg/kg on day 0 (HD) or 2 mg/kg on days 0, 2, 4, and 6 (LD). Von Frey was used to assess hypersensitivity, flow cytometry to characterize CD4+ T cells in the DRG, and immunohistochemistry to quantify nerve loss/CD4+ T cells in hind paw tissue. Although there was no statically significant difference in PTX-induced mechanical hypersensitivity with HD and LD regimens in male or female mice, each regimen promoted distinct CD4+ T cells in the DRG. Mice that received the HD regimen had significantly more anti-inflammatory CD4+ T cells in the DRG (female: IL-10, IL-4, and FoxP3 and male: pro-TGF-β) and reduced nerve loss in the hind paw compared to mice that received the LD regimen. Our results suggests that the clinical presentation of CIPN may be similar, but the mechanism driving the development/resolution may be dependent on hormones and the immune microenvironment. Understanding these complex relationships will better facilitate the development of targeted immunotherapies to treat CIPN.

Sex-Dependent Effects of Cannabidiol, Beta-Caryophyllene, and Other Cannabis-Derived Terpenes on Nociception and Body Temperature in Mice
Lida Khodavirdilou, Jenny Wilkerson; Texas Tech University Health Sciences Centerceutical Sciences

Cannabidiol (CBD) is studied for its therapeutic potential, while cannabis-derived terpenes are hypothesized to contribute to cannabis-related entourage effects. This study evaluated the antinociceptive and thermoregulatory effects of CBD, beta-caryophyllene, alpha-terpineol, and gamma-terpinene using a cumulative dosing protocol (56 to 320 mg/kg) in male and female C57BL/6J mice. Antinociception was assessed with the hot plate test, and thermoregulation was evaluated via rectal temperature measurements. Analysis revealed sex-dependent effects for both CBD and beta-caryophyllene in the hot plate test. Males exhibited significant antinociceptive effects at 320 mg/kg CBD, while females showed no significant changes. Beta-caryophyllene produced significant dose-dependent decreases in body temperature in both sexes. Alpha-terpineol did not significantly affect nociception but induced dose-dependent hypothermia at higher doses (320,178 mg/kg) in both sexes. Gamma-terpinene produced dose-dependent reductions in body temperature in male mice only. Control experiments with vehicle administration demonstrated stable responses in hot plate latency and body temperature across multiple injections, with no significant sex differences or changes from the baseline observed. When combined with CBD, each terpene produced augmented antinociception compared to CBD

alone. These findings highlight critical sex-specific responses to cannabinoids and terpenes, underscoring the importance of considering sex differences in the development of cannabis-based therapeutics. Funding: Supported by Texas Tech University Health Sciences Center Jerry H. Hodge School of Pharmacy Department of Pharmaceutical Sciences Startup Funding.

Sex Differences in Inflammatory Signaling in a Preclinical Model of Chronic Migraine
Kofi Frimpong-Manson, Jenny Wilkerson; Texas Tech University Health Sciences Center

Although neuroinflammatory changes appear to be important in migraine pathophysiology, it remains unclear if these changes are sex-linked. To explore potential sex differences in inflammatory markers, we treated male and female 8-week-old C57BL/6J mice with nitroglycerin (10 mg/kg) or saline on 5 alternating days, conducted the von Frey assay for hind paw mechanical allodynia, and the acetone evaporation assay for cold allodynia. Nitroglycerin-treated mice displayed robust, persistent mechanical allodynia. Cold allodynia was also observed. A separate group of mice underwent the same treatment paradigm, nitroglycerin-evoked pain was confirmed, and mice were euthanized on day 5. Plasma, cortex, and thalamus tissues were collected and analyzed using a Luminex assay to quantify immune markers. Specifically, we were interested in the following pro-inflammatory cytokines: interleukin-1-beta (IL-1β), interleukin-6 (IL-6), interferon-gamma (IFN-γ), interleukin-15 (IL-15), interleukin-5 (IL-5), and interleukin-2 (IL-2). We also studied the IL-2 receptor (IL-2R). IL-1β was significantly increased in the plasma of nitroglycerin-treated females, suggesting a heightened peripheral inflammatory response. In the cortex, IL-6 and IL-2 concentrations were decreased in nitroglycerin-treated females. IL-2R was increased in the cortex of nitroglycerin mice without sex difference. Interestingly, IL-6 was elevated in the cortex of nitroglycerin-treated males, hinting at a distinct maladaptive inflammatory profile from females. In the thalamus, IL-5 levels were reduced in nitroglycerin-treated females. This reduction suggests region- and sex-specific modulation of immune markers in migraine. Together, these novel findings highlight the importance of studying sex-specific neuroimmune mechanisms in migraine pathophysiology.

Prolactin Receptor Modulates Hypersensitivity in Female Mice Following Repeated Ischemia with Reperfusion Injury
Luis F. Queme, Meranda M. Quijas, Megan C. Hofmann, Michael P. Jankowski; University of New England

Myalgia is a common cause of disability, exercise intolerance, and emotional distress. One cause is ischemic injury, where reduced blood flow impairs oxygen supply to tissues. This injury is often seen in disorders like fibromyalgia and complex regional pain syndrome, which differentially affect males and females. In our model of prolonged ischemic myalgia in which mice experience repeated ischemia/reperfusion (I/R) injury, we identified female-specific sensitization linked to upregulation of interleukin 1 receptor type 1 (IL1r1) and transient receptor potential cation channel (TRPV1) in the dorsal root ganglia (DRGs). Affected muscle in females also exhibited higher interleukin 1 beta (IL1β) levels which was absent in males. These sex-specific differences in DRGs appear to involve the RNA-binding protein AU-rich element RNA binding protein 1 (AUF1), whose phosphorylation differs between sexes at baseline. The

hormone prolactin (PRL) has been shown to influence inflammatory pain in females and may regulate phosphorylation of AUF1. Using a Prlr antagonist, we observed reduced TRPV1, IL1r1, and phosphorylated AUF1 (pAUF1) upregulation in DRGs, along with partially blunted mechanical hypersensitivity after repeated I/R injury in females only. PRL binding its receptor activates the JAK/STAT pathway, which may mediate AUF1 phosphorylation. In our ischemic model, STAT3 expression significantly increased in females after repeated I/R injury, while Prlr antagonist administration prevented this rise. This study may highlight potential sex-specific mechanisms underlying chronic ischemic myalgia and could inform targeted interventions for females in the future.

Synovial Immune Cell and Growth Factor Differences Between Sexes in Osteoarthritis Pain States

Alison Guzzetti, Peter Giunta, SreeLakshmi Gurrala, Diana Goode, Tamara King; University of New England

Osteoarthritis (OA) is a degenerative joint disease causing severe pain and disability. Due to heterogeneity and complexity of OA pain, targeted treatments are lacking. Most common pain descriptions are mid-stage OA characterized by activity-related pain that dissipates with rest, and advanced OA pain described as development of a constant pain that does not dissipate with rest. Research shows females report more severe advanced OA pain than males despite similar pathology. Therefore, we hypothesize that differences in immune cells and the associated cytokines and growth factors within the synovial fluid underlie these sex differences in joint pain. Using the monosodium iodoacetate (MIA) rat model, we found females treated with 16 mg/ml MIA develop constant joint pain and weight asymmetry indicating advanced OA pain whereas males show weight asymmetry in the absence of constant joint pain indicating mid-stage OA pain. Synovial fluid was collected, and flow cytometric results showed no sex difference in the frequency of T-cells, neutrophils, or natural killer cells. However, females had a greater frequency of macrophages and B-cells compared to naïve females or males treated with 16 mg/ml MIA. Females treated with 16 mg/ml MIA had a decrease in the frequency of neutrophils and had elevated levels of VEGF-A compared to saline treated females. The higher concentration of VEGF-A and the increased frequency of macrophages and B-cells in females but not males correspond to sex differences in the pain phenotypes, indicating immune function as a potential mechanism contributing to the progression of OA pain.

Sex-specific Hippocampal Synaptic Dysfunction Relates to Sleep and Pain Changes in a Mouse Model of Chronic Inflammatory Knee Pain

Valeriia Stepanova, Angel-Rose Villegas, Noel Lefevre, Heidi Kloefkorn; Oregon State University

Chronic joint pain disproportionately affects females who experience poorer outcomes compared to males, including poor sleep. While the mechanisms are unknown, chronic pain often coexists with sleep disturbances that can exacerbate pain. These interconnected challenges may be rooted in common central neuroplastic changes within the hippocampus, a brain region important to pain modulation and sensitive to sleep disruption. This study elucidates sex-specific hippocampal

synaptic and sleep changes in a preclinical mouse model to begin identifying common mechanisms with chronic inflammatory joint pain. Male and female adult C57BL/6J mice received unilateral intra-articular knee injections of monoiodoacetate (MIA, n=11-14) or saline (n=13-16). At 8 weeks, hindpaw mechanical sensitivity, sleep staging, and terminal electrophysiology measures were taken. Hippocampus receptor-specific synaptic strength and axonal conduction were assessed via field excitatory postsynaptic potentials (fEPSP) and fiber volleys (FV), respectively. Receptor-specific antagonists were applied to isolate contributions of AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors) and NMDAR (N-methyl-D-aspartate receptors) to fEPSP and FV waveforms. Male and female MIA mice developed similar heightened hindpaw mechanical sensitivity relative to saline animals ($p<0.05$), but had distinct sex-specific differences in receptor responses and sleep patterns. Female MIA mice exhibited increased AMPAR responses and decreased NMDAR, and their subunit responses, while males showed increased NMDAR responses. In females, synaptic changes correlated with mechanical sensitivity ($p<0.05$) and trended with sleep changes ($p<0.08$). These results suggest synaptic changes play a more prominent role in female pain processing and sleep dysfunction rather than in males, revealing sex-specific mechanisms and potential therapeutic targets in chronic pain pathways.

The Effects of Race and Sex on Acute and Subacute Postoperative Pain Following Major Surgery

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Inadequately controlled postoperative acute pain is associated with poor patient outcomes and higher risks of chronic pain, which negatively impacts quality of life and mental health. Despite reports on undertreated postoperative pain in women and racial minorities, existing literature on the relationship of race and sex with postoperative pain is mixed, lacking sufficiently large studies with comprehensive data. We aim to characterize the effects of sex and race on postoperative pain severity and analgesic prescription and use. Data is collected from a prospective 2,500-patient perioperative study, P5 (Personalized Prediction of Persistent Postsurgical Pain). Ecological Momentary Assessments (EMA) are completed three times a day preoperatively and for 30 days postoperatively on measures such as pain and analgesic cravings. Preoperatively, demographic and behavioral data is collected, including on opioid use. Postoperatively, pain levels at rest and movement are reported. We plan to examine the effects of race and sex on postoperative measures, including average and worst pain intensity in the post-anesthesia care unit (PACU) and in-hospital, in-hospital analgesic use, and pain measures collected via EMA for 2 weeks after discharge. Preliminary data (n=303) indicates that Black race and female sex are independently associated with worse postoperative pain at rest ($p<0.001$ for both). Prior to the 2025 USASP meeting, we plan to conduct these analyses on the full cohort (n=2,500, expected recruitment by December 2024), and present results of pain and analgesic use outcomes, adjusting for demographic and socioeconomic covariates, type of surgery, and anxiety and depression scores, in multivariable regression models.

SREBP1c-Dependent Lipid Modification in the Insular Cortex Regulates Chronic Overlapping Pain

Mahadi H. Shahed, Hayelom Mekonen, Michael L. Keaser, Ohannes Melemedjian, Robert K. Ernst, David A. Seminowicz, Joyce T. Da Silva, Alison J. Scott, Richard J. Traub; University of Maryland School of Dentistry

Chronic pain, impacting 21% of adults in the U.S., remains a critical medical challenge with few effective therapies. Chronic overlapping pain conditions (COPCs), such as temporomandibular disorder (TMD), irritable bowel syndrome (IBS), and fibromyalgia, frequently co-occur, predominantly affect women, and are often worsened by stress. While peripheral mechanisms may underlie individual pain conditions, central nervous system dysregulation appears to play a key role in COPCs. Current therapies are insufficient, highlighting the need to target CNS pathways for effective intervention. This study seeks to identify novel, non-addictive pharmacological targets to alleviate COPC-associated pain using a rat model of comorbid pain hypersensitivity (CPH), in which orofacial pain and stress lead to chronic visceral hypersensitivity. We investigated brain activity and connectivity changes using fMRI and analyzed lipid and metabolite alterations by spatial lipidomics using mass spectrometry imaging (MSI) to identify molecular mechanisms underlying pain. Preliminary results revealed heightened visceral hypersensitivity in CPH rats, with fMRI indicating increased activity and disrupted connectivity in the insula cortex (IC), mPFC, and amygdala. MSI analysis revealed altered lipid profiles in the IC, particularly changes in fatty acid elongation and desaturation patterns. Since SREBP1c regulates key enzymes mediating fatty acid elongation and desaturation, such as ELOVL2, ELOVL6, and SCD, we targeted SREBP1c using siRNA in the IC. This intervention reduced referred pain by ~60%, establishing a mechanistic link between lipid metabolism and pain modulation. Our findings identify the IC and modulation of lipid populations as promising therapeutic targets for effective chronic pain intervention. Supported by R01DE029074.

Insular Cortex Functional Connectivity And Stimulus-Evoked Brain Activity Are Sex Dependent in a Rat Model of Chronic Overlapping Pain Conditions

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Temporomandibular disorder and irritable bowel syndrome are two chronic overlapping pain conditions (COPCs) that present with significant comorbidity. Both conditions are more prevalent in women and are exacerbated by stress. We developed a rat model of comorbid pain hypersensitivity (CPH). CPH rats were injected in the masseter muscles with CFA followed by 4 days of restraint stress. Stressed-Induced Hypersensitivity (SIH) rats were only stressed. CFA rats were injected with CFA only, and Naive rats received no injection nor were they stressed. All rats underwent MRI and mechanosensitivity testing for referred pain for 3 sessions: Baseline (pre pain/stress), 1 week post pain/stress, and week 7. MRI sessions consisted of 2 scans: resting-state and a stimulus-evoked scan using colorectal distension. Results revealed female CPH rats showed significantly greater widespread insula connectivity than male CPH rats at baseline, week 1, and week 7, including the primary and secondary somatosensory areas and prelimbic area. CPH resulted in greater functional connectivity to the insula compared to CFA and SIH rats at week 7. All female rats showed significantly greater distension-evoked brain activity

compared to males, including in the primary and secondary somatosensory areas and hippocampus. Female CPH rats exhibited significantly greater referred pain than males at week 7. Based on these findings, the insula connectivity pattern plays a key role in sex differences in comorbid pain and will be further investigated using mass spectrometry analysis. Identified changes in insula lipids and metabolites will help determine new therapeutic targets for chronic pain. Funding: R01DE029074.

Applying a Novel Whole Person Approach Findings Show Sex Differences in a Measure of Allostatic Load in Diverse Mid-Older Adults with Chronic Pain Associated with/risk for Knee Osteoarthritis

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Sex differences are evident across different levels of analysis in chronic pain. Research also indicates environmental, psychosocial, and behavioral factors influence pain-related health outcomes. Using a novel whole person approach to characterize individuals with chronic pain, we assessed sex differences in the relationship between a measure of whole person risk and allostatic load based on a clinical stress system composite (CSSC). Non-Hispanic black and non-Hispanic white adults 45-85 years old with > 1 chronic pain site(s) and a CSSC were included (n=191). The novel whole person assessment combined measures of chronic pain stage, socioenvironmental and behavioral factors with dispositional traits. Chronic pain stage which was determined by knee pain frequency, intensity, duration and total pain sites. Socioenvironmental factors included education, poverty level, Area Deprivation Index, marital, employment, and insurance status. Behavioral factors included tobacco use, exercise amplitude, optimism, perceived stress, social support, and sleep impairment. Variables were assigned 1 for risk or 0 for buffer based on evidence-based ranges and summed. Median low risk (0-7) and high risk (8-17) profiles were combined with vulnerable or protective dispositional traits resulting in four groups representing whole person risk (WPRG). The CSSC (0-10) was comprised of ten measures indicating cardiovascular, immune, metabolic, and neuroendocrine functioning. Adjusting for age, study site, comorbidities, and non-linear sex*WPRG interactions, with greater whole person risk, females had higher CSSC than men ($p<0.0048$). In diverse adults with chronic musculoskeletal pain associated with knee pain, findings indicate sex differences in a measure of allostatic load reflecting individual health status.

Sickle Cell Disease

Assessing the Impact ff Long-Term Hydroxyurea Treatment on Chronic Pain in Townes Sickle Cell Disease Mice

Nya Gayluak, Sourav Roy, Lindsey Ramos Freitas, Michael Burton, Katelyn Sadler; The University of Texas at Dallas

Pain is the primary reason individuals with sickle cell disease (SCD) seek medical care. Although some of this pain is linked to vaso-occlusion, more than 50% of patients also suffer from daily chronic pain. In addition to opioid-based analgesics, hydroxyurea is routinely

prescribed to individuals with SCD. Hydroxyurea is a disease-modifying therapy that reduces red blood cell sickling by increasing fetal hemoglobin (HbF) levels. Although hydroxyurea is administered to individuals with SCD as early as nine months of age, there has never been a systematic assessment of how lifelong hydroxyurea treatment influences chronic pain in SCD. Thus, in this study, we used the Townes SCD mouse model first to determine the age at which the chronic pain phenotype develops in these animals, and second, to determine how lifelong hydroxyurea impacts chronic SCD pain development. Our findings indicate that mechanical hypersensitivity develops in Townes SCD mice between three to four weeks of age following the fetal-to-adult hemoglobin switch, which occurs between postnatal days 0 and 5 (P0-P5). Furthermore, hydroxyurea treatment significantly reduces mechanical hypersensitivity in SCD mice at all time points tested. These findings contribute to the ongoing discussion among SCD patients and providers regarding preventative measures for the development of chronic SCD pain and provide further evidence for support of hydroxyurea use in individuals with SCD.Funding: [KS1] Rita Allen FoundationNIH R00HL155791

Investigating Chronic Pain Mechanisms in Adult Sickle Cell Disease Measured by Functional Connectivity - A Feasible Study

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Chronic pain in Sickle Cell Disease (SCD) negatively affects the quality of life, causing central sensitization and brain connectivity changes in regions tied to pain and cognition, and is difficult to clinically assess with subjective pain tools. Thus, we aimed to explore the hypothesis that patients with SCD and pain show altered connectivity in the default mode and salience networks. We utilized quantitative sensory testing (QST), brief pain inventory (BPI), and MRI to explore these connectivity differences. We enrolled four adults with SCD and five healthy controls (mean ages 30.25 and 28.2 years respectively) and pain (BPI: worst and least pain scores of 6.33±1.25 and 1.00±0.82). QST was conducted on the non-dominant forearm using a thermal probe to assess thermal detection(sensitivity-cold/warm) and pain thresholds(tolerance-cold/hot). While mean thermal changes varied from the baseline (32°C), differences between SCD and controls were insignificant. Functional connectivity was measured across QST conditions($p<0.05$ cluster size, family-wise error corrected). Patients with SCD showed reduced thermal sensitivity for detection thresholds but heightened sensitivity for pain thresholds. Compared to controls, patients exhibited reduced medial prefrontal cortex-left superior frontal gyrus (SFG) connectivity($p=0.012$) during cold detection but increased connectivity during cold pain. Warm detection increased anterior cingulate-right frontal pole connectivity($p=0.002$), while hot pain decreased right supramarginal gyrus-left cerebellar connectivity($p=0.0002$). The left SFG connectivity may reflect changes in pain intensity processing, while decreased cerebellum connectivity in SCD may stem from altered pain processing pathways. The sample size is a limitation of our study and will be addressed in future findings.

Whole Person Care Clinic for Youth with Sickle Cell Disease

Carmela Sambells, Elizabeth Bettini, Megan Connolly, Steven Hardy, Risi Idiokitas, Laila A.

Mahmood, Theodore Martinovich, Lisa Thaniel, Deepika S. Darbari; Children's National Medical Center

Sickle cell disease (SCD) affects over 100,000 individuals in the United States. While episodes of acute pain are the most common complication, over 50 percent of adults develop chronic pain which typically starts during adolescence and is associated with psychological comorbidities. Chronic pain can be treatment refractory. Pain interferes with daily functioning, leading to missed school/workdays, adversely affecting quality of life and attainment of life goals. Approximately 50 percent of adults living with SCD are un/underemployed with incomes below the federal poverty level. A comprehensive whole-person care approach initiated in childhood may improve pain outcomes and function in SCD. Integrative Health Clinic (IHC) was established at Children's National Hospital's Division of Hematology. Youth 8 years or older at risk for or diagnosed with chronic pain are referred to the clinic. After a comprehensive assessment, an individualized plan is developed with the patient/caregiver. Patients receive educational materials and clinical services from hematologists, psychologists/psychiatrists, school education specialists, non-pharmacologic mind-body specialists, physical therapists, and nutritionists, coordinated by a hematology nurse navigator. The social worker provides families with resources to address social determinants of health. Additional resources include peer mentoring and community-building activities. Since 2023, 46 patients have received services at least once. Of these, 32 eligible patients (age 8-17 y) have committed to longitudinal visits through enrollment in the Enhanced Integrative Health Clinic study (EIC). The IHC presents a unique model of whole-person care for youth with sickle cell disease at risk of developing or with chronic pain.Funding: Founders Auxiliary Board

Gut Microbiota and Metabolites on Chronic Pain in Sickle Cell Disease

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The neurobiology of chronic pain in sickle cell disease (SCD) remains poorly understood. This study aimed at evaluating the differences in the gut microbiota composition and gut-derived metabolites in a transgenic mouse model for SCD and its impact on SCD pain. We found significant differences in the alpha and beta diversity between the two cohorts and lower ASVs associated with Turicibacter, higher ASVs associated with Lactobacillus, Odoribacter and Monoglobus genera in the SCD mice relative to non-sickle controls. Additionally, significant difference in the gut-derived metabolites were observed as evidenced by distinct clustering on the principal component analysis, along with significant differences in metabolite groups of interest including short-chain fatty acids. Fecal material transplantation (FMT) from sickle to non-sickle mice resulted in mechanical allodynia, heat hyperalgesia, and cold allodynia. Additionally, FMT from SCD mice to wild-type mice was sufficient to evoke anxiety-like behaviors in the recipient mice as evidenced by decreased time spent in the open arm of the elevated-plus maze and decreased time spent in the central compartment in the open field test. Reshaping the gut microbiota of SCD mice with FMT from WT mice resulted in reduced mechanical allodynia thermal hyperalgesia and reduced anxiety-like behaviors. These findings provide novel insights into the relationship between gut microbiota and pain in SCD, highlighting the different gut microbial communities and metabolites which may serve as potential targets for pain management.

Acupuncture Modulates Brain Connectivity and Outcomes of Pain and Vaso-occlusive Crisis in Patients with Sickle Cell Disease

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Sickle Cell Disease (SCD) is a genetic blood disorder marked by chronic pain and recurrent painful episodes called vaso-occlusive crises (VOCs). Acupuncture has shown promise in reducing pain in conditions like fibromyalgia (FM) by modulating brain functional connectivity (FC), but its effects in SCD are unexplored. This single-blind RCT (NCT# 05045820) explored acupuncture's effects on pain and VOC outcomes as well as brain FC in 17 SCD patients (aged 18-73; Treatment A: n=7, Treatment B: n=10). Patients received acupuncture or mock laser (control), with groups labeled Treatment A and Treatment B to maintain blinding. fMRI was conducted during resting-state and tonic pressure-pain stimulation on the left gastrocnemius muscle. Treatment A showed greater improvements in pain and VOC outcomes than Treatment B including PainDetect scores assessing neuropathic pain prevalence ($t=-2.6$, $p=0.01$) and Adult Sickle Cell Quality of Life Measurement (ASCQ-Me) evaluating the severity of VOC in frequency/recency ($t=-1.8$, $p=0.05$). Seed(insula/somatosensory)-to-whole-brain FC analysis revealed decreased FC in Treatment B compared to Treatment A between the left insula and right precuneus during rest, and between the right insula and bilateral occipital poles during pressure-pain stimulation and when comparing pain stimulation to rest ($pFWE<0.05$). Decreased insula-DMN FC at rest suggest that Treatment B reduces resting FC between these regions, a pattern linked to reduced pain in FM. Meanwhile, Treatment A may improve pain outcomes by enhancing insula-sensory FC, reflecting sensory input from acupuncture in modulating pain processing. Ongoing analyses aim to validate these findings and explore associations with acupuncture analgesia in SCD.

Isolation and Molecular Characterization of Hippocampal and Cortical Neurons From Sickle Cell Mice

Yugal Goel, Kendall O'Daniel, Mya A. Arellano, Kalpna Gupta, Vidhya Kumaresan; University of California, Irvine

Chronic pain, central sensitization and cognitive impairment coexist in many hereditary blood disorders including sickle cell disease (SCD) but remain underexamined. These require a robust understanding of the neural mechanisms in different regions with specialized neuronal populations in the brain. Transgenic humanized mouse models offer preclinical insights into the mechanisms but remain challenged by the complexity of obtaining specific neuronal cells in culture from fragile mouse models such as those of SCD. We developed an optimized protocol for preparing cortical and hippocampal neuronal cultures from transgenic humanized mouse models of sickle cell disease that express >99% human sickle hemoglobin (HbS) and control mice expressing normal human hemoglobin A (HbA). Our method overcomes complexities posed by fragile transgenic mice strains. The use of laminin as a substrate for culturing the neurons allowed optimization of cell attachment, survival, dendritic arborization and synapse formation. Cultures are prepared from the dissociated cortex and hippocampus of postnatal day 0

- postnatal day 3 (P0-P3). These cells provide insights into the regulation of synaptic and homeostatic plasticity in sickle mice. We examined immunoreactivity of synaptic markers, including, vesicular glutamate transporter1 (VGlut1), postsynaptic density protein 95 (PSD95) and subunits of AMPA-subtype and NMDA receptor subtype (GluN1, GluN2B and GluN2A) of glutamate receptors with/without pharmacological interventions. Co-localization of glutamate receptor subtypes with PSD95 and VGluT1 are observed. The improved culture protocol thus enables more accurate studies of dendritic morphology and synaptic maturation, with implications for research on neuronal development, plasticity, and disease modeling.

Intestinal Microbiome Changes are Associated with Higher Rate of Acute Pain Events in Individuals with Sickle Cell Disease

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The biology of acute sickle cell disease (SCD) pain is incompletely understood. Dysbiosis, alterations in the intestinal microbiome, is a driver of chronic inflammation and may contribute to acute SCD pain. We hypothesized dysbiosis is associated with increased SCD pain frequency. Stool samples were collected from SCD patients and 16S rDNA sequencing was completed. The acute pain event rate (events/year) was determined and categorized into three groups: <1, ≥1 and <3, and ≥3. Alpha diversity (within samples) was assessed via Pielou Evenness (higher value represents increased evenness). Beta diversity (between groups) was assessed using Unweighted UniFrac metric. Alpha and beta diversity were compared between the three groups using Kruskal Wallis test (alpha diversity) and pairwise PERMANOVA (beta diversity). Significance, adjusted for false discovery rate, was set at <0.1. We enrolled 122 SCD patients; mean (SD) age 16.54 (12.69) years, 46% female. Alpha diversity was significantly lower in group with ≥3 events/year compared to group with <1 event/year (adjusted p=0.02), indicating lower evenness in those with more pain. Beta diversity was significantly different between group with ≥3 events/year and group with <1 event/year (adjusted p=0.06) and between group with ≥1 and <3 events/year and group with <1 event/year (adjusted p=0.06); indicating microbial community composition differences between groups. SCD patients with a higher pain rate have a less diverse microbiome. A distinct composition of microbial communities was seen between those with a higher compared to lower pain rate. These data suggest dysbiosis likely contributes to SCD pain biology.

Altered Resting-State Functional Connectivity in Sickle Cell Disease: Implications for Pain Sensitivity and Neural Adaptations

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Background:Chronic pain and cognitive dysfunction are common in Sickle Cell Disease and may be linked to disruptions in brain network connectivity. Resting-state functional connectivity studies provide critical insights into neural mechanisms underlying these symptoms, particularly

in networks associated with pain perception and emotional regulation.Methods:120 individuals were approached for participation, including SCD patients and healthy controls. Of these, 32 consented, and 12 were scanned, with 8 participants (SCD = 6, HC = 2) included in the analysis. The cohort (mean age: 31.8 ± 7.7 years; 100% Black) included 4 with HbSS, 1 with HbSC, and 1 with HbSβ°. Functional MRI data were preprocessed using CONN and SPM12 toolboxes. Preprocessing steps included realignment, slice timing correction, normalization to MNI space, and smoothing, followed by denoising with regression of confounding factors and bandpass filtering (0.01-0.08 Hz). Resting-state functional connectivity was assessed using ROI-to-ROI connectivity matrices and a general linear model. Group-level analyses examined differences in functional network connectivity with hierarchical clustering and cluster-level inferences ($p < 0.05$).Results:Healthy controls exhibited balanced connectivity with strong intra-network integration and inter-network segregation (Figure 1). In contrast, SCD patients demonstrated hyperconnectivity, characterized by widespread positive correlations and reduced anti-correlations (Figure 2). Disruptions were most pronounced in the default mode network, salience network, and sensorimotor regions.Conclusion:SCD patients exhibit significant alterations in resting-state functional connectivity, suggesting maladaptive neural mechanisms underlying chronic pain. Key regions, such as the anterior cingulate cortex and parahippocampal gyrus, may serve as biomarkers for disease progression and therapeutic targets.

Intestinal Microbiome Changes are Associated with Neuropathic Pain in Individuals with Sickle Cell Disease

Katelyn Sadler, Samantha N. Atkinson, Janelle Highland, Nicole Steiner, Jessica J. Rico, Dawn Retherford, Mehri Bagherimohamadipour, Jane S. Hankins, Hamda Khan, Michelle Brignac, Joshua Field, Ashmia Singh, Nita Salzman, Amanda M. Brandow; University of Texas at Dallas

Many individuals with sickle cell disease (SCD) live with chronic neuropathic pain that likely results from chronic inflammation. The mechanisms driving chronic inflammation in SCD are muti-factorial, but may include intestinal dysbiosis, an imbalance in the intestinal microbiome. To determine if changes in the intestinal microbiome are associated with neuropathic pain in SCD, we conducted a cross-sectional multi-site study. Individuals ≥14 years with SCD in baseline health were enrolled. Stool samples were collected, microbial DNA extracted, and 16S rDNA sequencing completed. All individuals completed the painDETECT questionnaire, a neuropathic pain screening measure. Beta diversity was assessed using Weighted UniFrac method and the Adonis multivariable permutation test was used to determine if the covariates of interest explained the observed microbiota variability within SCD patients. Covariates were collection site, age, sex, mode of birth (vaginal, c-section), infant feeding (formula, breastfed), relatedness, and painDETECT score. Significance level was $p<0.05$. We enrolled 54 SCD patients; mean (SD) age 26.2 (12) years, 57% female, SCD genotype was HbSS 57%, HbSC 35%, HbSβ0thal 2%, HbSβ+thal 6%. Beta diversity was significant. The painDETECT score explained a significant proportion of the intestinal microbiota variability within SCD patients ($R2=5.4\%$, $p=0.001$) after adjusting for site ($R2=2.4\%$, $p=0.043$), age ($R2=6.2\%$, $p=0.001$), mode of birth ($R2=3.4\%$, $p=0.011$), relatedness ($R2=68.8\%$, $p=0.002$), sex (not significant), and infant feeding (not significant). These data support the hypothesis that intestinal microbiota changes may drive neuropathic pain in individuals with SCD. Future work is focused on

identifying differentially abundant bacteria and microbial products that contribute to these findings.

Depression and Anxiety are Significantly Associated with Worse Pain-related Patient-reported Outcomes in Individuals with Sickle Cell Disease

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Acute and chronic pain are common complications of sickle cell disease (SCD), and depression and anxiety are co-morbid conditions in those with chronic illness. We sought to determine whether increased depressive and anxiety symptoms are associated with pain-related patient-reported outcomes (PROs) in individuals with SCD. Individuals age ≥8 years with SCD were included. Participants completed Patient Reported Outcomes Measurement Information System (PROMIS) self-report measures of Depression, Anxiety, Pain Interference, and Pain Behavior. Primary predictor variables were depression and anxiety. Primary outcomes of individual multivariate models were Pain Interference and Pain Behavior. Covariates of interest were age, sex, genotype, and Area Deprivation Index (ADI). Relationships between depression, anxiety and the primary outcomes were assessed via multivariate regression while controlling for the described covariates. Study cohort included 100 SCD patients (n=41 adults, n=59 children). Mean (SD) age was 21.1 (11.79) years and 49% were female. Genotype was 64% HbSS, 28% HbSC, 1% HbSβ0thal, and 7% HbSβ+thal. Higher Anxiety scores were significantly associated with higher Pain Interference scores ($p=1.24x10-6$) after adjusting for covariates. Depression scores were not associated with Pain Interference scores ($p=0.271$). Higher Depression and Anxiety scores were significantly associated with higher Pain Behavior scores ($p=0.004$ and $p=0.029$, respectively) after adjusting for covariates. Older age was significantly associated with higher Pain Behavior scores ($p =1.31x10-5$). Sex, genotype, and ADI were not significant. Patient-reported depression and anxiety symptoms are significantly associated with worse pain-related PROs in individuals with SCD. Addressing mental health as part of a comprehensive pain management plan is vital.

Caregiver Awareness Of Omega-3 As A Complementary Pain Treatment For Youth With Sickle Cell Disease

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Randomized controlled trials have indicated that omega-3, a healthy dietary fatty acid, reduces pain frequency and inflammation in youth with SCD. Despite evidence of it as a promising complementary pediatric SCD pain treatment, there is limited information on omega-3 consumption knowledge among caregivers of youth with SCD, and rates of consumption among youth with SCD. The current study examined caregiver knowledge of and attitudes toward SCD-related omega-3 benefits, and consumption among youth with SCD. Forty-one caregivers of youth (aged 5-17) with SCD were recruited from VCU's Pediatric SCD clinic. Age, gender, SCD genotype, and hydroxyurea use were confirmed via medical chart review. Percentages and means

were calculated for each scale. Approximately 74% of caregivers reported they had not heard of omega-3 as a complementary pain treatment option, and 79% were unaware that omega-3 reduces the frequency of pain episodes. While 51% of caregivers report youth taking any dietary supplement, only 4 caregivers (10%) reported their youth took an omega-3 supplement in the last week. Fifteen caregivers (37%) reported their youth takes a multivitamin with omega-3; however, only 4 (10%) report daily use. Higher knowledge scores among caregivers were associated with higher omega-3 consumption among youth ($r=0.35$, $p<.05$). The findings highlighted the lack of awareness of omega-3 benefits among caregivers of youth with SCD. These findings indicate a need for dissemination of information to the SCD community to raise awareness of Omega-3 as an evidence-based complementary treatment option for pediatric SCD pain. Funding: Society of Pediatric Psychology Grant.

Levagen+ Ameliorates Hyperalgesia In A Mouse Model Of Sickle Cell Disease
Donovan Argueta, Bryant Avalos, Natalie Garcia, Yannick Fotio, Daniele Piomelli, Nicholas DiPatrizio, Kalpna Gupta; University of California, Irvine

Sickle cell disease (SCD) is an autosomal recessive inherited disorder of the ß-globin gene resulting in sickle hemoglobin (HbS). Unpredictable, episodic acute pain is unique to SCD, requiring hospitalization, opioid use, and reduces survival; additionally, individuals may experience persistent chronic pain. Palmitoylethanolamide (PEA) is an endogenous paracannabinoid mediator of neuropathic pain and inflammation. Using humanized, transgenic BERK mice expressing human sickle hemoglobin which show hyperalgesia similar to features of chronic SCD pain and controls expressing normal human hemoglobin A, we observe a reduction of spinal PEA concomitant with chronic hyperalgesia in sickle vs control mice. Administration of Levagen+, an orally bioavailable micronized PEA preparation, ameliorates hyperalgesia, improves hematological parameters, and reduces inflammation in sickle mice. Mice were treated for 14 days with Levagen+ (oral, 300 mg/kg/d) or vehicle (sterile phosphate-buffered saline), and measures for chronic and acute (incited by hypoxia/reoxygenation) mechanical, cold, and musculoskeletal hyperalgesia were evaluated. Whole blood, plasma, organs, and skin biopsy-conditioned media (releasate) were collected to assess pharmacokinetics, hematology, pathology, and inflammation at endpoints. Levagen+ significantly increased plasmatic PEA 1 hour following treatment (~85%, $P<0.01$), at which time, measures of hyperalgesia were significantly reduced ($P<0.05$), which continued to improve during 14-day treatment. Levagen+ ameliorated acute pain, improved red blood cell (~40%, $P<0.05$) and hemoglobin levels (~37, $P<0.05$), reduced liver size (~30%, $P<0.05$), and reduced markers of inflammation in plasma and releasate ($P<0.001$). These results suggest that Levagen+ targets mechanisms of inflammation to improve analgesia and hematologic parameters in SCD and may be a safe, accessible treatment option.

The Impact of Sleep on Pain Sensitization in Youths with Sickle Cell Disease
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Sickle cell disease (SCD) is an inherited blood disorder characterized by acute pain crises and heightened prevalence of chronic pain. Approximately 30-40% of pediatric patients with SCD

have chronic pain, contributing to poorer physical and mental health outcomes. Central sensitization (CS; central nervous system hyperexcitability) may heighten chronic SCD pain, yet few investigations have examined factors related to CS in youths with SCD. To address this, our study examined the role of sleep, a modifiable factor associated with pain, in relation to CS in 55 participants (26 boys: mean age=16.43 years) with severe genotypes of SCD (Hemoglobin type SS n=54, type S beta-zero thalassemia n=1). Mean-level and within-person variability sleep indices were measured at-home over 7 days using wrist actigraphy and daily diaries. To measure CS, participants completed one session of quantitative sensory testing (QST). Conditioned pain modulation (CPM) assessed endogenous pain inhibition and temporal summation (TS) assessed pain facilitation using both heat (TS-heat) and mechanical (TS-mechanical) stimuli. Multilevel models predicted pain ratings during each task. When controlling for age, sex assigned at birth, and task unpleasantness, lower actigraphy-derived sleep efficiency predicted worse pain inhibition during CPM and greater pain facilitation during TS-mechanical. No other sleep parameters predicted QST task performance. Findings provide further evidence that poor sleep efficiency may be linked to enhanced pain via impaired pain inhibition and pain facilitation but may be best captured using objective sleep measures in pediatric SCD. Funded by the University of Mississippi Department of Pediatric Intradepartmental Discovery Support Program.

20-Hete: An Emerging Target to Improve Pain Sensitivity in Sickle Cell Disease
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Acute or persistent pain are the most imperative comorbidity in sickle cell disease (SCD) resulting highest number of emergency visits and hospitalization. The premature hemolysis of the sickle red blood cells associated with a downstream cascade of vaso-occlusion and multiorgan damage traditionally attributes to ischemia and nociception in the musculoskeletal system. The SCD pain involves peripheral nociceptor sensitization of the transient receptor potential vanilloid 1 (TRPV1) in the form of hyperalgesia and allodynia. Elevated circulating heme, byproduct of intravascular hemolysis, is implicated for multiorgan injuries and genesis of SCD pain. Despite the epidemiological link between pain and kidney injuries, the mechanism linking these two complications in SCD is unknown. We discovered that heme induces 20-hydroxyeicosatetraeonic acid (20-HETE), an arachidonic acid metabolite, in renal tubular epithelial cells following heme-induced kidney injuries in SCD mice. We hypothesize that elevated circulating 20-HETE generated during acute hemolysis aggravates pain sensitivity in SCD. We discovered that plasma 20-HETE is significantly elevated in mouse and human with SCD compared to normal controls. Heme-induced kidney injuries led to heightened renal expression of CYP4A12A, the enzyme responsible for producing 20-HETE. Subsequently, expression of TRPV1 was elevated in the dorsal root ganglia. Microvascular constriction with increased expression of angiotensin II receptor-1 and the 20-HETE receptor GPR75 associated with reduced blood flow were evident in the kidneys and thigh muscles of the SCD mice following heme challenge. Overall, our data show that elevated 20-HETE may exacerbate pain sensation via systemic endothelial dysfunction and microvascular congestion. Funding: 1R01 DK124426; 1R01 DK132145.

Elevated Heme Inhibits Sensory Neuron Slo1 BK Channels To Cause Evoked And Ongoing Pain In Sickle Cell Disease.

Samuel Zorn, Vanessa Ehlers, Anvitha Sriram, Jonathan Enders, Cheryl Stucky; Medical College of Wisconsin

Elevated Heme Inhibits Sensory Neuron Slo1 BK Channels To Cause Evoked And Ongoing Pain In Sickle Cell Disease.Authors: S. J. Zorn, V. L. Ehlers, A. Sriram, J. Enders, C. L. StuckyDepartment of Cell Biology, Neurobiology & Anatomy, Medical College of Wisconsin, Milwaukee WIIndividuals with sickle cell disease (SCD) suffer from complex stimulus-evoked and ongoing pain that is mediated in part by the hyperexcitability of their peripheral sensory neurons. However, it is unclear whether acute or chronic elevation of cell free heme, a key pathological feature of SCD, contributes to the aberrant activity of sensory neurons. In the current experiments, we demonstrate that peripheral injection of heme in WT mice causes acute behavioral sensitivity to mechanical and thermal stimuli while driving learned place aversion and ongoing distress. We reveal that circulating heme readily perfuses the dorsal root ganglia to embed within the cell bodies of primary sensory neurons. As intracellular heme is a potent regulator of potassium ion conductance, we use patch clamp electrophysiology to determine that the large conductance calcium-activated potassium channel, Slo1 BK, is inhibited by heme incubation in vitro. Finally, we demonstrate that pharmacological rescue of BK channel activity by the channel opener NS 11021 in vivo alleviates steady-state pain-like behaviors in SCD mice. These results suggest a central role for heme-dependent signaling in the maintenance of SCD pain and illuminate downstream effectors that may be targeted to provide analgesic relief for this historically understudied and debilitating disease. Funding: F30 HL170558.

Intersectional Stigma, Pain, and Coping: Insights from Black Adults with Sickle Cell Disease

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Stigma is common among adults with sickle cell disease (SCD), contributing to worse pain outcomes. However, few studies have explored experiences of intersectional stigma (i.e., based on multiple identities within the context of overlapping oppressive systems) in this population. We conducted semi-structured interviews with 27 Black adults (67% women, mean age = 35.85) with SCD to explore how intersectional stigma impacts pain and their strategies to cope with stigma. We transcribed interviews, and coding and analysis are ongoing. We will use an inductively developed codebook to code and conduct content and thematic analyses. We have identified three preliminary themes. (1) Participants reported a range of acute and chronic pain experiences, but most participants experienced substantial pain that interfered with their functioning and generally worsened with age. (2) While experiences of SCD-related stigma varied, most participants reported experiencing considerable stigma in emergency rooms, including being disbelieved about having SCD and the severity of their pain. SCD-related stigma was compounded by race-related stigma and led some participants to avoid emergency room care, favoring at-home, non-medical pain management. (3) Participants described various methods for coping with stigma, including seeking family and friend support, religious and

spiritual practices, mindfulness and acceptance exercises, or taking direct action to change the situation through self-advocacy. This preliminary data suggests that intersectional stigma negatively impacts pain management among Black adults with SCD, and individuals use several coping strategies to manage these stigmatizing experiences. Future research should develop and test stigma-reduction interventions in SCD, ultimately improving pain outcomes.

Lysophosphatidic Acid Signaling Contributes to Acute Pain Accompanying Vaso-Occlusive Crisis in a Model of Sickle Cell Disease

Iryna Khasabova, Fuad Abdulla, Malcolm Johns, Annabelle Herold, Kathy Tang, Viacheslav Viatchenko-Karpinski, Sergey Khasabov, Kalpna Gupta, John Belcher, Gregory Vercellotti, Donald Simone; University of Minnesota

Lysophosphatidic Acid Signaling Contributes to Acute Pain Accompanying Vaso-Occlusive Crisis in a Model of Sickle Cell DiseaseThe hallmark of sickle cell disease (SCD) is severely painful vaso-occlusive crises (VOCs). Exposure to cold is a common trigger of VOCs. Unfortunately, the mechanisms and key mediators contributing to pain in VOCs are not understood. Exposure to cold (10°C for 1 hour) was used to evoke painful VOCs in transgenic mice with SCD (HbSS), and produced acute spontaneous nocifensive behavior (SNB) and hyperalgesia. SNB was assessed by grimace and body posture. Mechanical hyperalgesia was defined as a decrease in paw withdrawal threshold using von Frey monofilaments. Heat hyperalgesia was defined as a decrease in paw withdrawal latency to radiant heat. Importantly, cold-induced acute pain was accompanied by hypoxia, vaso-occlusion, red blood cell sickling and hemolysis - all clinically relevant symptoms of VOCs in patients. We found a 10-fold increase in the level of lysophosphatidic acid (LPA), a well-known pain mediator, in the blood of HbSS mice after cold exposure. Intrathecal administration of LPA1 receptor siRNA prevented cold-induced SNB and hyperalgesia in HbSS mice. Patch-clamp recording from acutely dissociated small DRG neurons from hyperalgesic HbSS mice revealed sensitization of small DRG neurons, defined as a decrease in inactivating and non-inactivating outward currents, more positive resting membrane potential, lower rheobase, and higher duration and frequency of action potentials. These parameters were normalized by blocking or knocking down the expression of LPA1 receptors. Our data demonstrate that LPA is a mediator of VOC pain in SCD.

Alteration of Cortical Activity in Patients With Sickle Cell Disease Experiencing Vaso-occlusive Crisis: An Exploratory Study With a Portable Electroencephalogram Device

Pangyu Joo, UnCheol Lee, Andrew Pucka, Richard Harris, Ying Wang; University of Michigan

Sickle Cell Disease (SCD) is a genetic hematological disorder characterized by chronic pain, recurrent vaso-occlusive crises (VOCs, also known as pain crises), and other comorbidities. Earlier we showed that explosive synchronization, a marker of brain network sensitivity collected from a high-density 32-channel EEG is associated with the timing of VOC. This study investigated alterations in alpha wave frequency (7-13 Hz), a cortical activity marker, in SCD patients using recordings from both a 32-channel EEG and the portable 4-channel Muse2 device (TP9, AF7, AF8, TP10) to assess the feasibility of tracking cortical activity using portable EEG device.Analysis of 32-channel EEG prior to- or during-VOC recordings from 25 SCD patients

revealed significantly lower alpha band frequencies as (9.01 ± 0.42 Hz) compared to 18 matched healthy controls (9.83 ± 0.59 Hz, $p < 0.00001$). A similar trend of reduced alpha frequencies was observed in the Muse2 dataset, with SCD patients exhibiting lower frequencies (8.78 ± 0.44 Hz) compared to healthy controls (9.37 ± 0.34 Hz). Importantly, Muse2 alpha frequency measurements strongly correlated with those from the 32-channel system ($p < 0.001$), demonstrating the potential of portable EEG for monitoring brain activity in SCD.These findings indicate that SCD is associated with reduced alpha wave frequency, reflecting potential neurological changes. The strong agreement between high-density and portable EEG supports the feasibility of using portable devices for longitudinal monitoring cortical activities associated with onset and progression of VOC in SCD. Future studies with larger sample sizes are needed to validate these exploratory findings.

In-home Virtual Reality versus Audio Control for Chronic Pain in Adults with Sickle Cell Disease: A Randomized Trial
Nadine Matthie, Melinda Higgins, Coretta Jenerette; Emory University

Many adults with sickle cell disease (SCD) experience chronic non-vaso-occlusive pain in addition to SCD pain or pain crises. Because pain management is often reported as inadequate or ineffective, self-management is vital. Virtual reality (VR), which has shown benefits in other chronic pain conditions, may be beneficial for adults with SCD. This study was conducted to: (1) assess feasibility of using an in-home, VR pain management intervention (EaseVRx) versus audio control (Audio) for self-management of chronic pain among adults with SCD, and (2) evaluate preliminary effects on pain and pain-related outcomes. In this parallel group, randomized trial using surveys and interviews, 44 participants (19 VR and 25 Audio) completed 2-16-minute daily modules for 8 weeks, daily pain diary surveys, surveys about chronic pain grade and chronic pain correlates every 4 weeks for 3 months, and a post-study interview. Feasibility outcomes of enrollment, survey response, intervention use, and cybersickness were all achieved, and participants rated the interventions as acceptable. Between baseline and week 12, significant improvements were seen for pain intensity ($p = .002$), pain catastrophizing ($p = .005$), and chronic pain acceptance ($p = .002$) in both groups. Higher VR dose was associated with larger decreases in pain intensity levels from baseline to week 8 (Spearman's rho = -0.786, $p = .036$). There were improvements in VR sleep impact scores ($p = .009$) and Audio stiffness impact scores ($p = .026$). Mixed results regarding cybersickness and effects suggest that additional research, with larger sample sizes, is needed. NIH 5R21NR019872-02.

Sleep and Pain

Cyclical Changes in Sleep and Pain in Temporomandibular Disorder
Francis Westbrooks, Luana Colloca, Akintola Titilola, Yang Wang; University of Maryland

Temporomandibular disease (TMD) is a prevalent condition linked to chronic pain and sleep disturbances, both of which may fluctuate with seasonal changes.1,2 While prior research suggests cyclical patterns in sleep and pain, the relationship between sleep and pain across seasons remains unclear. This study examined seasonal shifts in sleep patterns and chronic pain among 277 TMD patients enrolled between June 2017 and January 2020. Total sleep time (TST)

was recorded based on self-reported sleep and wake times, while sleep efficiency (SE) was calculated as the proportion of actual sleep to time in bed. Current pain severity was measured using the Graded Chronic Pain Scale. Seasonal decomposition analysis was performed to examine periodic changes in TST, SE, and current pain severity. The analysis revealed seasonal components explaining 19.27% of the variance in TST, 27.03% in SE, and 21.81% in pain, indicating moderate periodic fluctuations across all variables. Trend analysis suggested that chronic pain peaked, and sleep efficiency decreased in winter. Notably, a significant negative correlation ($r = -0.53$, $p = 0.002$) was observed between the seasonal components of SE and pain severity, and the seasonal component of TST and pain severity ($r = -0.42$, $p = 0.016$), suggesting an inverse dynamic of seasonal patterns of sleep efficiency and pain severity. This study highlights seasonal fluctuations in sleep and pain severity among TMD patients, underscoring the influence of cyclical changes on these conditions. Understanding these patterns could inform tailored management strategies to address the dynamic needs of TMD patients throughout the year.

Effects of Acupuncture on Sleep and Fatigue in Older Adults with Chronic Low Back Pain: Findings from the BackInAction Pragmatic Clinical Trial

Christina Mu, Andrea Cook, Lynn DeBar, Vicki Li, Alice Pressman, Lisa Dean, Arya Nielsen, Morgan Justice, Andrew Avins, Katie Stone; University of California

Chronic low back pain (cLBP) is a debilitating condition that affects approximately one-third of older adults. Pharmacological intervention may have adverse consequences (e.g., drug interactions, increased risk of falls). Acupuncture is an effective intervention for cLBP that may have additional beneficial effects apart from pain control. This abstract examined the effects of acupuncture on sleep outcomes and fatigue. The BackInAction study is a multi-site, three-arm randomized trial that examined the effectiveness of acupuncture needling: 1) standard acupuncture (15 sessions across 12 weeks), 2) enhanced acupuncture (standard acupuncture and 6 additional sessions), and 3) usual medical care. This abstract includes 743 of the 800 older adults with cLBP (≥65 years M(SD)=73.7(5.9) years; 62% female; 17% with high sleep disturbance) who completed at least one outcome assessment at 3, 6, or 12 months. Linear regression models were conducted with GEE to handle correlation due to multiple outcomes per participant and acupuncturist. Analyses controlled for baseline outcomes, demographics, and pain characteristics associated with missing outcomes. Results revealed no differences in PROMIS sleep quality or sleep duration. However, at 6 months, compared to the usual-medical-care group, those in the enhanced acupuncture group had slightly longer sleep duration (0.2 hours difference, p=.06). At 12 months, those in the enhanced acupuncture treatment group had lower fatigue (-2.3 difference, p=0.001) relative to usual medical care. Study findings suggest acupuncture may improve sleep and fatigue in older patients with cLBP.

Examining the Additive Impact of Human Immunodeficiency Virus and Insomnia on Sleep Difficulty and Pain Sensitivity

Caroline Webb, Shannon Gilstrap, Joanna Hobson, Halla Stallworth, Dyan White, Shameka Cody, S. Justin Thomas, Robert Sorge, Burel Goodin; The University of Alabama at Birmingham

People with HIV frequently report sleep difficulties and daily pain that, together, significantly impacts their quality of life. Although the bidirectional relationship between sleep and pain is well-established, the impact of HIV status and insomnia on pain remains less understood. This study examined the additive effects of HIV (HIV+ vs. HIV-) and insomnia status (insomnia+ vs. insomnia-) on sleep difficulty and pain sensitivity using experimental quantitative sensory testing (QST). Participants completed eligibility screening, the Insomnia Severity Index (ISI), QST procedures, and actigraphy across two research visits (N=136). Participants comprised four subgroups: HIV-/insomnia- (n=46), HIV-/insomnia+ (n=37), HIV+/insomnia- (n=14), HIV+/insomnia+ (n=39). Results revealed an additive effect of HIV and insomnia status, such that the HIV+/insomnia+ group reported the greatest degree of sleep difficulty on the ISI and demonstrated the lowest actigraphic sleep efficiency compared to the other groups. Furthermore, the HIV+/insomnia+ group demonstrated the greatest temporal summation of mechanical pain and the least conditioned pain modulation effect via QST compared to the other groups. It appears that the combination of HIV and insomnia may promote experimental pain sensitivity. Future research should examine whether non-pharmacologic treatments such as Cognitive Behavioral Therapy for Insomnia might improve pain sensitivity via improved sleep for people with HIV.

Pain and Stress Influence Sleep Differently in Chronic Pain

Autumn Rajcevich Schwer, Giselle McPherson-Isbell, Steven Miller, Joanna Buscemi, Rachel Greenley, Susan Tran; DePaul University

There are cyclical relationships between stress and pain, and between pain and sleep, and stress exposure can be detrimental to sleep health. Our study analyzed how stress impacts sleep health in individuals with chronic pain. Forty-three emerging adults who self-reported chronic pain wore an ActiGraph watch for 14 days to assess objective sleep health and completed the Pittsburgh Sleep Quality Index daily to assess subjective sleep quality, the PHQ-15 to assess pain symptoms, and a daily hassles questionnaire. Regarding objective ActiGraph sleep measurements, daily hassles were negatively correlated with total sleep time, $r= -0.36$, $p = 0.03$. Regarding subjective sleep quality, hassles were positively correlated with daytime dysfunction $r= 0.41$, $p= 0.007$. Hassles showed trends towards being significantly correlated with sleep quality (higher scores reflect worse sleep), $r= 0.26$, $p= 0.09$, sleep duration (higher scores reflect worse sleep), $r= 0.26$, $p= 0.09$, and sleep disturbance, $r= 0.26$, $p= 0.09$. Surprisingly, hassles just missed significance on the correlation with PHQ scores, $r= 0.28$, $p= 0.07$; however, PHQ symptoms were related to worse subjective sleep disturbance, daytime dysfunction, and total sleep score (all $p<0.05$). Interestingly, individuals reporting higher stress objectively demonstrated less total sleep time but did not subjectively report significantly worse sleep. However, those with more pain symptoms subjectively reported significantly worse sleep. Individuals with higher pain symptoms may be more aware of sleep disturbance, potentially attributing it to nighttime pain. Stress and pain may impact sleep health in different ways, and more research with subjective and objective measures is needed.

Assessment Of Risk Factors For Development Of Persistent Postsurgical Pain: Sleep

Disturbance

Joel Hanns, Harutyun Alaverdyan, Simon Haroutounian; Washington University in Saint Louis

The development of Persistent Postsurgical Pain (PPSP) is associated with a complex nexus of factors, including but not limited to sociodemographic, clinical history, neurocognitive factors. Personalized Prediction of Persistent Postsurgical Pain (P5) collects robust data on a diverse set of surgical patients before, during, and after surgery to elucidate factors that may be of interest in the study of PPSP. An often-overlooked factor in postoperative pain is sleep. Previous work establishes a bidirectional relationship between sleep quality and pain. Preliminary assessment of the first 400 patients in study showed a significant association between two different preoperative self-report measures of sleep quality and persistent, clinically meaningful pain at 3 months after surgery. Preoperative PROMIS sleep disturbance scores were significantly higher in patients who reported PPSP (pain at surgical site with intensity >3 on 0-10 scale at rest) after three months (55.6 [52.6-58.5]) compared to those that did not (51.9 [50.9-52.8]) ($p<0.05$, n=382). Patients were also asked to rate their sleep quality in daily ecological momentary assessment (EMA) surveys several days prior to surgery. When comparing the average of EMA surveys, the scores of sleep disturbance were significantly higher in those that reported PPSP (43.4 [35.0-51.8]) compared to those that did not (28.7 [26.0-31.4]) ($p<0.02$, n=352). Both the PROMIS and EMA measures of sleep disturbance correlate positively with each other ($r2=0.336$). Recruitment is ongoing, and we plan to present expanded data with multivariable logistical regression controlling for sociodemographic and neurocognitive factors of approximately 2,000 participants at the USASP conference.

Uncovering Sleep Determinants of Clinical Pain Severity Through Machine Learning

Eric Duan, Nandini Raghuraman, Yang Wang; University of Maryland

Sleep quality and pain are closely related, with poor sleep quality being a critical predictor of worsening pain. However, the relative impacts of subjective sleep experience, objective sleep measures, and mood alternations from sleep require further investigation to assess which metric has the most influence on pain. Machine learning is a powerful tool to capture the complex multidimensional relationships between sleep and pain. This secondary data analysis utilized data from 617 adults with and without sleep apnea from the Cleveland Family Study to identify the most important sleep factors in predicting clinical pain. We included objective measures of sleep such as sleep duration, latency, and apnea severity, subjective measures such as self-reported post-sleep activity and vigilance levels, and sociodemographic factors such as age and family income. Pain severity was measured using the bodily pain subscore from the Short Form 36 (SF-36) questionnaire. We utilized elastic-net regression (ENR), random forest (RF) and gradient boosted regression (GBR) for feature selection and model performance comparisons. ENR was the most predictive model, outperforming RF and GBR and explaining around 28% of pain variance using sleep metrics. Subjective assessments of activity and vigilance emerged as among the most important factors in the ENR model in predicting pain severity, followed by sociodemographic factors and psychological metrics of health. The findings highlight the importance of subjective sleep quality compared to objective measurements and demographic variables when predicting clinical pain. Further research should investigate the mechanisms through which sleep influences pain.

Ecological Momentary Assessments of Sleep Disruption, Opioid Craving, and Opioid Use Motivation in Chronic Low Back Pain

Patrick Finan, Liza Abraham, Matthew Reid, Michelle Mei, Siny Tsang, Jim Stone, Johannes Thrul, Andrew Huhn, Kelly Dunn, Michael Smith; University of Virginia School of Medicine

Sleep disturbance and opioid craving are potential targets of intervention to prevent and treat problematic opioid use among patients with chronic pain. This study investigated microlongitudinal associations between sleep disturbance, prescription opioid craving, and opioid use motivation among participants with chronic low back pain (CLBP) on long-term opioid therapy (N=81). Participants completed 14 days of ecological momentary assessments, which included morning and evening surveys. Sleep disturbances were assessed in the morning as wake after sleep onset (WASO - in mins) and number of nocturnal awakenings; opioid craving was assessed in the morning as urge to use opioids throughout the night (i.e., nocturnal craving) and, separately, the next evening as urge to use throughout the day; opioid use motivation was also assessed in the evening as a composite score measuring wanting to use opioids, wanting to avoid opioids, and perceived ability to control one's opioid use. Generalized linear mixed effects models revealed both WASO ($p<.001$) and nocturnal awakenings ($p<.001$) were strongly associated with greater nocturnal opioid craving, and WASO predicted greater odds of daytime opioid craving ($p=.02$). In turn, both nocturnal craving ($p=.02$) and daytime craving ($p<.001$) were associated with greater opioid use motivation. Mediation analysis indicated that there were significant indirect effects of WASO on opioid use motivation via both nocturnal craving (95%CI: .03-.11) and daytime craving (95%CI: .04-.12). Collectively, these findings indicate that sleep disruption may be an important upstream contributor to risk for problematic opioid use in patients with CLBP on long-term opioid therapy. Funding: NIH/NIDA R01DA048206.

Objective and Subjective Sleep of Individuals With and Without Chronic Pain

Giselle McPherson-Isbell, Autumn Rajcevich Schwer, Joanna Buscemi, Susan T Tran, Steven A Miller, Rachel N Greenley; DePaul University

Sleep problems are common among individuals with chronic pain, as pain both contributes to and results from poor sleep. Individuals often inaccurately estimate their sleep compared to objective measures. This study compared the concordance between objective and subjective sleep measures in individuals with and without chronic pain. The study included undergraduate students--43 with self-reported chronic pain and 122 without. Participants wore an ActiGraph watch for 14 days to objectively assess sleep quality and completed the Pittsburgh Sleep Quality Index to measure perceived sleep quality. Measures included sleep duration, sleep efficiency, sleep disturbance, and total sleep score. An r-to-z transformation compared correlations between the groups. A significant relationship was found between objective and subjective sleep duration in participants with chronic pain ($r = -0.38$, $p < .01$, indicating a higher concordance),but not in those without chronic pain ($r = -0.14$, $p = .14$). The group difference was not significant ($Z = 1.27$, $p = .10$). Correlations for objective and subjective sleep efficiency and fragmentation were non-significant in either group($p > .05$). Subjective sleep disturbance and objective wakings after sleep onset were not significant in either group (chronic pain $r = .16$, $p = .31$, no pain $r = -.15$, p

= .11),however the comparison was significant (Z = 1.68, p = .0465). While overall concordance was poor, chronic pain participants may report sleep issues more accurately. Given that recall was poor in undergraduates, objective sleep measures are important. Future studies should explore how different sleep measures relate to functional outcomes.

Investigating Sleep Quality in a Rodent Model of Low Back Pain
Lydia Saltz, Ariel Ammentorp, Evie Reddick, Anjeza Erickson, Hannah White, Angel-Rose Villegas, Heidi Kloefkorn, Rebecca Wachs; University of Nebraska-Lincoln

Chronic low back pain (LBP) is a leading cause of disability worldwide, with 88 % of affected individuals reporting sleep disruption. Growing evidence suggests a strong, reciprocal relationship between sleep and pain, suggesting that sleep may serve as a valuable metric for predicting the onset and modulation of pain. However, the specific nature of the relationship between sleep and chronic LBP has yet to be characterized in a preclinical model. Our lab has previously established a disc-associated LBP model in rats with high fidelity to the human condition. We implemented a noninvasive sleep system that captures sleep metrics in the home cage, reflecting features similar to humans. Utilizing this system, sleep changes and pain-like behavior (pressure algometry) were monitored at baseline and 3, 5, 7, 9, 11, 13, and 15 weeks post-injury with injury consisting of six bilateral scrapes to the L5-L6 disc (n=12 sham/injured; female/male). Pressure algometry at 8 weeks revealed a significant pain phenotype that persisted until week 15. At week 15, declines in sleep quality-characterized by increased fragmentation-were strongly correlated with worsening pain-like behavior (p=0.0371, n=7 females). Although group averages of the currently analyzed subset of sleep measures have not yet shown statistical significance, these findings suggest that pain-like behavior may precede changes in sleep quality. Ongoing analysis of the remaining animals will provide further insights into this crucial relationship. This is the first evidence of sleep changes in a preclinical LBP model using a novel method of sleep recording in rats. Funded by NIH (NS065926, R01AR080926).

Prevalence and Correlates of Poor Sleep Quality in a Sample of Minoritized Older Adults with Chronic Pain
Daniel Whibley, Kimberlydawn Wisdom, Sheria Robinson-Lane, Susan Murphy, Robin Brewer, John Piette, Mary R. Janevic; University of Michigan

African American older adults disproportionately experience poor sleep. Given reciprocal relationships between sleep and pain, sleep improvement may be an important aspect of chronic pain management interventions tailored for this community. As a first step in investigating sleep health needs in this population, we assessed prevalence and correlates of sleep quality in a sample of primarily (82%) African American adults age 50+ (mean 67 years) with chronic musculoskeletal pain (n=383). Data came from baseline assessment of a randomized trial of a pain self-management intervention (STEPS) delivered by community health workers in an underserved urban setting. We used chi-square analysis to determine associations between poor sleep quality (PROMIS Sleep Disturbance item; “very poor”/“poor”) with age (<64 years vs. 65+), gender, economic hardship (“very” or “extremely” difficult time paying bills each month),

high pain interference (PROMIS; “quite a bit” or “very much”) and high pain intensity (7+ on a 0-10 numeric rating scale). Overall, 38% of participants reported poor sleep. Participants aged <64 vs. 65+ were more likely to have poor sleep (45% vs. 33%; p=.013); as were those with vs. without economic hardship (60% vs. 33%; p<.001), high vs. low pain interference (51% vs. 26%, p<.001) and high vs. low pain intensity (47% vs. 29%, p<.001). Poor sleep was common in this sample and strongly linked to economic hardship and pain. Future analyses will determine if the pain-focused STEPS intervention, which includes sleep hygiene education, improves both sleep and pain outcomes among minoritized older adults. Funding: National Institute on Aging (R01AG071511).

Pleiotropic Prioritization: Unraveling Shared Genetic Threads in Insomnia and Chronic Pain Through an Advanced Gene Prioritization Pipeline
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Many chronic pain patients report co-occurring sleep disturbances, like insomnia, which have been linked to chronic pain development and exacerbation. Though these complex conditions frequently co-occur, it is unclear whether these are distinct conditions or whether a common mechanism may underlie development of both. Using a bioinformatics approach, we identified potential pleiotropic genes associated with both phenotypes. First, we developed a pipeline to prioritize genes implicated via single nucleotide variants (SNVs) associated with either insomnia or chronic pain phenotypes in genome-wide association studies (GWAS). Using the Functional Mapping and Annotation database, FUMA v1.5.6, we identified genes associated with our phenotypes of interest and mapped these to their mouse orthologs using the DRSC integrative ortholog prediction tool (DIOPT v9.0). We further searched for phenotypes of interest resulting from gene knock-outs in mice from the International Mouse Phenotype Consortium (IMPC) database. We then mapped prioritized gene product interactions using StringDB (v. 2.14.3). Interaction maps were identified for both human and mouse. Filtering using Pharos drug target database (v 3.19.1) resulted in 32 gene products with known drug targets. Using previously published whole genome-sequencing data generated from multiple inbred mouse strains, we identified 4 genes from our prioritized list that contained genotypic differences between substrains. We selected the gene Grik2, glutamate ionotropic receptor kainite type subunit 2, for further analysis. This pipeline facilitates the generation of novel hypotheses centered around common genetic mechanisms of risk for insomnia and chronic pain. Follow-up studies examining how Grik2 influences both insomnia and chronic pain are warranted.

How Does Multisite Chronic Pain Impact Pain, Sleep Quality, and Fatigue in Adolescents?
Chasity Brimeyer, Stacy Peterson, Nina Linneman, Theresa Kapke, Monica Gremillion, Kim Anderson Khan, Kevin Berridge, Rachel Schmidt, Yan Ke, Steven J. Weisman, Keri Hainsworth; Medical College of Wisconsin

The bidirectional sleep/chronic pain relationship is well-established, yet the influence of multisite pain (MSP) is less so. This study examined the impact of MSP on variables known to influence the sleep-pain relationship in adolescents with chronic pain. Participants (N=336; 13-19 years; 73% female; 86% White) presenting to a multidisciplinary pediatric pain clinic

completed measures of pain (Pain Frequency-Severity-Duration), behavioral sleep quality (Adolescent Sleep-Wake Scale), fatigue (PROMIS), and pain-related cognitive intrusion (CI; Experience of Cognitive Intrusion of Pain). Pearson correlations and Kruskal-Wallis tests were used to characterize the relationship between MSP and study variables. Overall, moderate pain intensity (M=5.7/10, SD=2.0), pain frequency (M=10.6 days/14, SD= 4.1), and sleep quality (M=3.1/6, SD=0.74) were observed, along with mild fatigue (M=54.8, SD=14.7). Females endorsed more MSP than males (p=0.016). White adolescents endorsed more MSP than Black adolescents (p=0.006). MSP was associated with more frequent pain (r=0.30, p<.0001), longer usual-pain duration (r=0.28, p<.0001), and greater worst-pain intensity (r=0.17, p=.0024). MSP was associated with better sleep quality (r=0.23, p<.0001) and sleep initiation (r=0.26, p<.0001). Conversely, MSP was associated with not feeling rested (r=-0.21, p<.0001) and increased fatigue (r=0.34, p<.0001). MSP was not associated with bedtime readiness or pain-related CI. MSP has a differential impact on aspects of adolescents' pain experience, sleep quality, and fatigue. Unexpectedly, MSP and better sleep were correlated. Experiencing pain in multiple areas may facilitate more opportunities to practice pain coping. Simply having pain may impact behavioral factors (e.g., bedtime readiness, intrusive thinking) irrespective of number of pain sites present.

Electroencephalography Obtained During Nocturnal Awakenings in Chronic Low Back Pain: A Methodological Proof-of-Concept

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Frequent nighttime awakenings, initiated by pain, are a chief complaint amongst chronic pain patients, and may lead to the engagement of maladaptive cognitive processes, which prolong the awaking and contribute to sleep loss. EEG sampled during these periods of wake after sleep onset (WASO) could therefore provide novel and transformative insights into sleep-pain interactions contributing to chronic pain. We obtained two nights of two-channel (AF8 & AF7) wireless sleep-EEG from participants with chronic low back pain (N=152). WASO was manually scored in 30s epochs, concatenated into a continuous time-series, and cleaned of artifact. Multi-taper spectral analyses were used to calculate power spectral density (log10*μv/Hz2) across the 4Hz-35Hz WASO spectrum, aggregating into Theta [5-8Hz], Alpha [8-13Hz] and Beta [15-34Hz] bands. Associations with next-day pain-related variables were tested with linear regression. Of the original sample, 107 nights of EEG records met final quality criteria for use in analyses. Adjusting for age and sex, WASO-Beta power [13-34Hz] was associated with increased intrusive thoughts about pain during the night (p<0.001), and racing thoughts during the night (p = 0.020 to 0.049) as well as increased pain interference (p = 0.036), and expectancy (p = 0.046) during the daytime. These findings illustrate a novel method of WASO-EEG assessment that reveals associations between nocturnal beta-power, and self-reported nocturnal pain-related cognitive hyperarousal, made retrospectively. WASO-EEG offers an alternative approach to understanding the mechanisms of sleep disturbance and pain, compared to traditional sleep-EEG and future work should consider its scalability and concordance with clinical pain outcomes.
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Sleep Hygiene Associated with Pain Presentations Among Orthopedic Surgical Patients
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Sleep hygiene is a modifiable factor that influences inflammation and pain sensitivity. Despite being modifiable, sleep hygiene is rarely assessed preoperatively and may be a driver of the relationship between poor sleep quality and pain response in surgical patient populations. This analysis examined the association between sleep hygiene habits and both pain and sleep quality preoperatively. Participants undergoing orthopaedic surgery on their upper extremity were recruited in this study approximately 2 weeks before surgery. Participants completed surveys including the Sleep Hygiene Index, PROMIS Sleep Disturbance, and PROMIS Pain Interference preoperatively. In addition, participants wore an actigraphy device (ActiGraph LLC) on the wrist that measured sleep efficiency and total sleep time over the two weeks prior to surgery. Linear regressions examined the association between baseline sleep hygiene scores and pain interference, sleep efficiency, and total sleep time. Regression models showed that poorer sleep hygiene (e.g., higher scores) were associated with worse PROMIS Pain Interference T-scores. In addition, participants with worse Sleep Hygiene scores had worse Sleep Efficiency (B= -0.213; 95% CI: -0.41, -0.014; p= .0371) and had fewer minutes in their Total Sleep Time (B=-8.91; 95% CI: -17.10, -0.72; p= .0341). This analysis found there is an evident relationship between poorer sleep hygiene and both increased pain interference and poorer quality of sleep. This study is among the first to examine the possible contributions of sleep hygiene on both patient-reported outcomes and objective measures of sleep among patients undergoing orthopaedic surgery in an ambulatory setting.

Associations Between Preoperative Actigraphy Sleep Measures And Acute Postsurgery Pain Intensity Among Adolescents: A Preliminary Investigation
Ana Carney, Cornelius Groenewald; Stanford University School of Medicine

Preoperative sleep disturbance is associated with increased postoperative pain, yet few studies have examined associations between actigraphy-derived sleep measures and postoperative pain intensity. Therefore, we conducted a prospective, observational cohort study to determine whether preoperative actigraphy-derived sleep measures predicted acute post-surgical pain intensity in adolescents. Primary predictors including total sleep time, sleep efficiency, and wake after sleep onset were measured before surgery using wrist-worn actigraphy. The primary outcome measure was pain intensity (0-10 numeric rating scale) measured daily during the first 14 days following surgery, including average and maximum daily pain intensity. Participants included 63 children, with a mean age of 14.9 years (range 11-19 years). Multivariate linear regression analysis estimated associations between predictor and outcome variables, controlling for biological sex (male/female), race, ethnicity, and surgery type. We found that actigraphy-derived lower sleep efficiency (β= -0.15, p=0.036) and greater wake after sleep onset (β=0.03, p=0.023) (but not total sleep time) were associated with significantly increased maximum daily pain intensity during the first 14 days following surgery. However, actigraphy-derived sleep measures were not associated with mean daily pain intensity over the first 14 days following

surgery. We conclude that preoperative sleep discontinuity is associated with greater maximum daily pain intensity following outpatient orthopedic surgery in adolescents. Therefore, preoperative actigraphy-derived sleep monitoring may identify patients at greater risk for poorer postoperative outcomes, including greater pain intensity, greater analgesic needs, and delayed recovery. Funding: R01HL166337

Assessing Sleep Quality in a Pilot Sample of Chronic Pain Patients: A Comparative Study of PSQI and OURA© Ring Measures

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This study focuses on two critical aspects of health and well-being in middle-aged and older individuals: sleep quality and pain. The study compares two contrasting yet complementary methods of evaluating sleep quality. The first is the Pittsburgh Sleep Quality Index (PSQI), a validated self-reported measure that is commonly used in sleep research. The second is the OURA© Ring, a piece of wearable technology that collects objective sleep data. The study uses baseline and post-intervention data from a pilot clinical trial. The participants in this trial were persons with chronic musculoskeletal pain (defined as pain greater than 4 out of 10 during the past 3 months on most days) and self-reported sleep disturbance (PSQI score>5, n=33). The study estimated measures and components equivalent to the PSQI questionnaire based on the objective OURA© ring data to evaluate whether self-reported sleep was reflected by objective sleep states and patterns. The results showed statistically significant correlations between several pairs of sleep measures from the PSQI and their equivalents from the OURA© Ring. However, the PSQI did not capture the number of nights where sleep latency exceeded 30 minutes. Therefore, the PSQI provides reliable surrogates of certain components of poor sleep duration and quality but not sleep latency, sleep efficiency, and sleep disturbances. The research underscores the importance of integrating subjective and objective measures in sleep research. It contributes to a comprehensive understanding of sleep quality assessment among aging populations experiencing chronic pain. Future studies are necessary to determine the causes of these discrepancies between subjective and objective sleep measures that may lead to improved methods for assessing sleep quality in persons with chronic pain. Funded sources**:** NIH/NIA grants: UF CTSI Pilot Grant UL1TR001427, UF CAMPAS Pilot Grant P30AG059297, UF Pepper OAIC Pilot Grant P30AG028740

Substance Use and Addiction

Transcutaneous Electrical Nerve Stimulation Use for People with Opioid Use Disorder for Reduction of Pain, Craving, Withdrawal: A Pilot Study

Barbara St. Marie, Jamie Morton, Carol Vance, Shaoshuai Chen, Yelena Perkhounkova, Jihye Lee, Peter Abad, Maria Hein; University of Iowa

Transcutaneous Electrical Nerve Stimulation (TENS) was examined to determine if craving, withdrawal, pain severity and pain interference is reduced in people with opioid use disorder (OUD) undergoing buprenorphine treatment. Of two million U.S. people with OUD, one-third are treated pharmacologically including buprenorphine. However, even with optimal

buprenorphine administration, half the patients have unsuccessful outcomes measured by withdrawal, craving, treatment retention, and taper. Grounded in neural mechanisms of pain/addiction, delta opioid-receptor activity mediates addictive behaviors (drug-seeking, impulsivity, loss of control over intake). TENS reduces pain via descending inhibitory pathways releasing serotonin, endogenous opioids, and Gamma-aminobutyric acid. This prospective pilot study proposed to measure feasibility and preliminary effectiveness of TENS on pain, opioid withdrawal and craving for 6-weeks. Participants were recruited from two midwestern facilities to use TENS (100Hz, 100us) while receiving buprenorphine for OUD treatment. Data was collected at baseline, weeks 1,2,4,and 6. Interviews completed week 6. Wilcoxon signed rank test detected variable changes from baseline to week 6, $p<.05$. There were 19 participants, 12 females, 14 White, 4 Black/African American, 2 Hispanic, mean(SD) age 49 years(15.4), OUD duration before treatment 9.9 years(9.6), 2 years(3.2) duration on buprenorphine. Preliminary results showed reduced craving from mean(SD): 4.4(2.8) to 2.3(2.8) ($p=.022$). Withdrawal reduced from mean(SD): 8.3(5.3) to 4.0(4.2) ($p<.001$). Pain severity and interference reduced. Interviews revealed symptom changes from TENS, TENS is useable and acceptable for treating OUD, and recommended strategies based on 6-week use. TENS shows promise as adjunctive treatment for people receiving buprenorphine for OUD to reduce craving, withdrawal, and pain.

Patterns of Cannabis Use in a National Sample of Patients Prescribed Long-Term Opioid Therapy for Chronic Pain

Natassja Pal, Meike Niederhausen, Siting Chen, Hannah Flegal, Travis Lovejoy, Steven Dobscha, Benjamin Morasco; Oregon Health & Science University

Cannabis use is common among individuals experiencing chronic pain, with 20-40% of patients prescribed long-term opioid therapy (LTOT) estimated to have concurrent use. With expanded cannabis legalization, more people are accessing cannabis products with the intent of independently treating health conditions and symptoms, including pain. However, empirical data about patterns of cannabis use and its impact on function are limited. We recruited a national sample of patients (n=511) who were prescribed LTOT for chronic pain and reported past-month cannabis use. Participants described cannabis use characteristics, including routes of administration (e.g., smoking, vaping, edibles, topicals), ratios of THC to CBD, frequency of use, and reasons for use. A latent class analysis characterized cannabis use in the sample and indicated three unique groups: 53.4% of the sample predominately smoked cannabis and reported mixed medical and recreational use, 15.3% endorsed multiple routes of administration and mixed medical and recreational use, and 31.3% reported mainly non-smoking routes of administration and cannabis use primarily for medical purposes. Study results also revealed that these three groups had significant differences in cannabis use characteristics, including frequency of use, quantity of product used, and reasons for consumption. These findings contribute to our understanding of cannabis use characteristics in a national sample, and can help inform personalized medicine approaches for patients experiencing chronic pain and using cannabis products. Future analyses will examine how pain, quality of life, and mental health variables differ across these groups. Funding: R01DA048817

Characterizing Treatment Needs Of Individuals With And Without Chronic Pain History Entering Drug Treatment Court Programs

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One in 4 individuals incarcerated in the United States experience chronic pain (CP), and individuals with CP on probation report more drug-related arrests and substance use than those without CP. Therefore, an effective treatment option for these individuals may be Drug Treatment Courts (DTCs), which address addiction needs as an alternative to incarceration. While individuals with CP, substance use, and criminal legal issues may be eligible for DTCs, little is known about their treatment needs. These secondary analyses compared treatment needs of those with and without CP across two SAMHSA-funded studies providing wraparound services alongside DTCs. Univariate and bivariate analyses of Government Performance and Results Act (GPRA) measures were used to characterize treatment needs for 170 new DTC participants with CP history (n=61) and those without (n=109). Participants were classified as having CP history if they reported CP and/or prescriptions for CP in their lifetimes. Within 30 days before assessment, participants with CP history reported more days of oxycodone use (0.05 vs. 0.00; p=.017) and opioid overdoses (0.12 vs. 0.00; p=.023) than those without CP history. Greater proportions of participants with CP history also reported: (1) opioid prescription misuse (66% vs. 16%), (2) prescription opioid use interference with responsibilities (56% vs. 16%), (3) withdrawal symptoms after stopping prescription opioids (59% vs. 12%) and (4) failures stopping prescription opioid use (67% vs. 17%; all ps<.001). Individuals with CP history have more addiction treatment needs entering DTCs, and they may need additional support with early recovery compared to those without CP history.

A Community Engaged Project: Patient Experience and Gaps in Chronic Pain Care from the Perspective of People with Prescribed or Nonprescribed Opioid Use

Michele Buonora, Christin Veasley, Robert Kerns, William Becker; Montefiore Medical Center & Albert Einstein College of Medicine

Background: Higher scores on patient experience measures - capturing patient interactions with clinicians and staff to assess aspects of care such as care coordination and communication - correlate with treatment guideline adherence and better outcomes. However, little is known about the patient experience of those with prescribed or non-prescribed opioid use seeking care for chronic pain - a group uniquely stigmatized in healthcare. Understanding their experiences could identify ways to improve care. Further, to date, studies have not been co-designed with patients and other relevant partners, ensuring patient centricity.Aims: To explore and assess gaps in the chronic pain clinical encounters, according to people with lived experience of prescribed or non-prescribed opioid use.Methods: Using a community engaged research (CEnR) framework, a diverse team of patients, veterans, insurers, clinicians and scientists co-designed a mixed methods study using survey and semi-structured interview techniques. Surveys, adapted from the Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey and revised through cognitive interviews, will compare participants' "best" and "worst" chronic pain clinical

encounters. Study participants include adults (>18 years) with chronic pain (>3 months) and self-reported opioid use (prescribed or nonprescribed for >6 months), recruited from the National Survivors Union and American Chronic Pain Association. A subset (N=20) will complete semi-structured interviews.Results: Data collection is currently ongoing.Conclusions: A CEnR framework is essential to ensure pain research aligns with the priorities, goals and concerns of those most impacted, and assessing patient experiences provides valuable insights to improve chronic pain care delivery.

"Cancer is Different:" Exploring Perspectives of Cancer Survivors on Long-Term Opioid Therapy for Pain

Maggie Nguyen, Whitney Redemer, Hope Cooley, Teri Dulong-Rae, Dace Svikis, Taylor Crouch; Virginia Commonwealth University

As cancer remission rates improve, a growing number of patients remain on opioids for pain management, which can complicate care and incur risks with prolonged use. This qualitative study explored the experiences of cancer survivors on long-term opioid therapy (LTOT), focusing on barriers and facilitators to reducing opioid use or transitioning to non-opioid alternatives. Adult participants with a history of cancer (currently non-active) on LTOT were recruited from a large, urban Cancer Center at an academic medical center. Using a semi-structured interview template, two focus groups (N=10; 5 participants each) were conducted. Focus groups were transcribed and analyzed using rapid qualitative analysis by two researchers to identify emerging themes. The sample consisted of 6 men and 4 women; 8 Caucasian and 2 Black. Seven themes emerged: (1) Perspectives on non-pharmacological chronic pain interventions, (2) Positives and negatives regarding opioid therapy, (3) Barriers and facilitating factors for seeking non-opioid treatments, (4) Experience of opioid-related stigma, (5) Perceived support from medical providers, (6) Barriers and facilitating factors for opioid reduction/tapering, and (7) Other perspectives on lived experience coping with pain. Patients shared both concerns and benefits of opioids, unique aspects inherent to cancer pain, stigma's impact on treatment, views on non-opioid treatments, and a need for more varied treatment options. Lived experience from cancer survivors on LTOT highlighted complex challenges, emphasizing a need for patient-centered approaches, reduction of opioid-related risks, and addressing of stigma. Enhanced support for non-opioid options could improve outcomes for this growing population.

Cannabis Use Patterns Among Veterans With Chronic Pain

Tristin Smith, Catherine Klida, Vivian Kurtz, Poonam Purohit, Anne Arewasikporn, Jennifer *Eckersley, Mia Railing, Riley Wegryn-Jones, Daniel Whibley, Anna Kratz, Amy Bohnert1, Rachel Bergmans, Kevin Boehnke;* University of Michigan

Cannabis Use Patterns Among Veterans With Chronic PainTristin Smith, Catherine Klida, Vivian Kurtz, Poonam Purohit, Anne Arewasikporn, Jennifer Eckersley, Mia Railing, Riley Wegryn-Jones, Daniel Whibley, Anna Kratz, Amy S. B. Bohnert, Rachel S. Bergmans, Kevin F. Boehnke;

University of MichiganAbstract:Chronic pain affects Veterans at a higher rate than the general population leading many veterans to explore alternative pain management strategies. However, little is known regarding how this population is engaging with cannabis, including preferred routes of administration, cannabinoid use, and overall use for pain. We utilized data from 143 participants (mean age (SD) 56.1 (13.6) years, 75.5% male; 76.9% non-Hispanic White) from the MIVetsCan Registry who reported 14,962 instances of cannabis use. Overall, edibles were the most common route of administration, with 69.2% of participants reporting use, followed by smokable bud/flower (50.3%), vaped concentrate/extract (28.0%), tinctures (21.7%), and topicals (19.6%). Less commonly reported methods including vaped bud/flower, dabs, capsules, suppositories, and beverages were reported by <5% of participants. The most common reported cannabinoids were Δ9-tetrahydrocannabinol (Δ9-THC, 74.8%), cannabidiol (CBD, 69.2%), cannabigerol (CBG, 12.6%), and cannabinol (CBN, 11.9%). Furthermore, 92.5% of incidents of participant-reported cannabis uses were for pain; 89.3% of these were reported as helpful for pain. Our findings describe how Veterans are engaging with cannabis products. Insight into how this population is utilizing these products can help inform clinician and patient education. This work was supported by the State of Michigan Veteran Marijuana Research Grant Program (VMR2022-03).

The Bidirectional Relationship Between Pain And Tobacco Use: Insights From The Population Assessment Of Tobacco And Health Study

Gabriel Costa, Julio Nunes, Rebecca Suh, Mehmet Sofuoglu, Joao P. De Aquino; Yale School of Medicine

Tobacco smoking remains the leading preventable cause of death in the U.S., while chronic pain is the primary driver of disability. Although convergent evidence links chronic pain and smoking, their causal and temporal dynamics remain unclear. This study utilized eight years of longitudinal data from the Population Assessment of Tobacco and Health study to explore whether pain predicts the onset of daily cigarette smoking and whether daily smoking contributes to the development of pain. Among 32,320 adult participants, we examined whether baseline pain (≥4 on a 0-10 scale) predicted transition to daily smoking among those who did not smoke, and whether baseline daily smoking predicted development of pain among those with no/low pain (0-3). Analyses accounted for alternative tobacco product use, gender, age, and race/ethnicity. Survival analysis of 5,731 individuals with complete data who did not smoke at baseline revealed that baseline pain significantly increased the risk of transitioning to daily smoking ($HR = 2.29$, $p < 0.001$). Similarly, among 12,099 individuals with no/low pain at baseline, daily smoking was associated with an increased risk of developing persistent pain ($HR = 1.87$, $p < 0.001$). These findings highlight a bidirectional relationship between chronic pain and tobacco cigarette smoking, emphasizing the need for integrated strategies to prevent and mitigate the development of persistent pain and smoking behaviors early. Funding: K23DA052682, R21DA057240, R01DA600066, VISN-1 Mental Illness Research Education and Clinical Center.

Preoperative Substance Use: A Risk Factor For Increased Post-Surgical Opioid Use Among

Adolescents
Rebecca L. Flack, Andrew H. Rogers, Jennifer A. Rabbitts, Tonya M. Palermo, Cornelius B. Groenewald; Stanford University School of Medicine

Among the over 1.8 million adolescents undergoing surgery in the U.S. annually, greater post-surgical opioid use has been associated with increased risk of opioid misuse. In teens, preoperative substance use has been identified as a potential risk factor. We sought to better understand this relationship within a cohort of 131 adolescents (10-19 years) undergoing surgery at a large children's hospital. We hypothesized that high-risk preoperative substance would be associated with greater total opioid use post-surgery, even when controlling for pain intensity. Self-reported preoperative substance use was determined using the Brief Screener for Tobacco, and other Drugs (BSTAD). Opioid use was tracked using a smart bottle cap device for 14 days after surgery, and pain intensity (0-10 NRS) was measured 4 times daily. In our sample, 11% of adolescents had high-risk substance use before surgery. Total opioid use in the 14 days following surgery followed a Poisson distribution. Consistent with our hypothesis, more opioid doses (12.2 doses) were taken on average in the 14 days following surgery by participants with pre-operative high-risk substance use compared to participants who reported low or no substance use at baseline (5.6 doses). In a multivariate Poisson regression model controlling pain intensity, demographic and psychological factors, and surgery type, opioid use remained significantly more likely among participants who reported high-risk substance use (1.45-2.26, $p<0.0001$). Future research will determine whether high-risk substance use is associated with opioid misuse at one year following surgery.

Unrelieved Pain and Risk of Opioid Use Disorder or Overdose in Older Adults Prescribed Opioids
Yu-Jung Jenny Wei, Siegfried Schmidt, Roger Fillingim, Guy Brock, Stephan Schmidt, Almut Winterstein; The Ohio State University College of Pharmacy

It is unclear to what extent unrelieved pain, the most common motive for prescription opioid misuse, is associated with risks of opioid use disorder (OUD) and opioid overdose (OD) among older adults with prescribed opioids. This retrospective cohort study was conducted among Health and Retirement Study (HRS) participants with linked Medicare claims data between 2006 and 2021. Participants aged 65 years or older with chronic pain who had received at least 1 opioid prescription entered the cohort in an HRS-assessed pain assessment (index) between 2008 and 2020. We included two time-varying measures of HRS-assessed pain exposure: uncontrolled pain, defined as having moderate or severe pain, and high-impact pain, defined as having moderate to severe pain that impacted daily activities. Primary outcomes of incident OUD or OD diagnosis were analyzed using separate Cox regression models with marginal structural modeling (MSM). Of 3104 eligible participants identified, 1359 (43.8%) had uncontrolled pain and 1044 (33.6%) experienced high-impact pain in the index wave. In the MSM-adjusted Cox regression model, patients with uncontrolled (vs controlled) pain had higher risks of OUD (adjusted hazard ratio [AHR] 9.70; 95% confidence interval [CI], 4.56-20.63]) and OD (AHR 2.46; 95% CI 1.30-4.66). The AHR for OUD was 6.74 (95% CI 3.76-12.08) and for OD was 1.96 (95% CI 1.07-3.60) times higher for patients with vs without high-impact pain. Our findings underscore the

importance of regular assessment and modification of pain management for older patients whose pain remains unrelieved after opioid treatment, to lower the risk of OUD and OD.

Evaluating Opioid Induced Hyperalgesia in Chronic Knee Pain

Kyle Diep, Kyaw Lin; Touro University College of Osteopathic Medicine

Opioid-induced hyperalgesia (OIH) presents a paradoxical increase in pain sensitivity resulting from prolonged opioid use, creating significant challenges in chronic pain management. This poster explores the case of a 79-year-old female with chronic bilateral knee pain exacerbated by opioid use, ultimately leading to a possible diagnosis of OIH. With a history of barbiturate and methadone use, there is a possible association with increased pain sensitivity, potentially exacerbating their overall discomfort. Treatment focused on the combination of gabapentin and corticosteroid injections (CSI) to alleviate pain and reduce opioid dependence. Gabapentin was utilized for its efficacy in targeting neuropathic pathways, while the CSI provided anti-inflammatory attributes for localized relief. The patient showed significant pain improvement throughout the treatment process that allowed for opioid tapering. This case study signifies the importance of multimodal treatment approaches in managing OIH, highlighting gabapentin and CSI as potential options for improving patient outcomes in chronic pain and opioid management.