Junior Investigator Poster Abstracts

(Listed in alphabetical order by Presenting Author)

Poster 1. – Mitchell Max Award Finalist. - Session 3: May 25 – 11:40am

Cryotherapy and Compression Therapy to Prevent Chemotherapy Inducted Peripheral Neuropathy in Breast Cancer Patients.

Melissa K. Accordino MD MS, Shing Lee PhD, Shiun Leu Cheng, Lauren Franks MS, Alessandra Taboada, Erin Honan, Cynthia Law MPH, Meghna Trivedi MD MS, Kevin Kalinsky MD MS, Katherine D. Crew MD MS, Dawn L. Hershman MD MS.

Background: One of the most common and debilitating adverse effects of curative breast cancer (BC) therapy is chemotherapy-induced peripheral neuropathy (CIPN). Taxanes are frequently used for early-stage breast cancer (ESBC); however, up to 81% of patients treated with taxanes experience CIPN. CIPN typically presents as distal sensory neuropathy and patients commonly report pain and/or paresthesias. CIPN is difficult to prevent and treat, and there are no effective prevention strategies that have been identified. Despite the known survival benefits of taxanes in ESBC, this treatment is often avoided, reduced, delayed, or discontinued due to CIPN, resulting in suboptimal BC treatment. It is critical to identify novel therapies to prevent and treat this common toxicity.
Cryotherapy and compression therapy are promising interventions for CIPN prevention. Both result in vasoconstriction which limits blood flow to the extremities. This mechanism is effective in the reduction of chemotherapy-related alopecia when applied to the scalp (using cryotherapy). Small non-randomized studies in patients with BC, have shown both cryotherapy and compression therapy to potentially be effective for CIPN prevention. However, is unknown which therapy, if either, is more effective at prevention of CIPN compared to placebo. In addition, patients serving as their own controls may have introduced reporting bias.

Objective: We are conducting a randomized phase IIB *adaptive sequential clinical selection trial* of subjects with ESBC during taxane chemotherapy treatment (NCT03873272). The total number of subjects to be enrolled will vary between 45 and 100 with an *expected sample size between 60 and 70* subjects for most likely scenarios. Participants will be randomized in triplets to either frozen gloves/socks (cryotherapy), compression gloves/socks (compression therapy), or "loose" gloves/socks (placebo arm). The primary goal of this study is to *select the best intervention* to be carried forward to a larger phase III trial, with a high probability of *correct* selection if one intervention is truly superior by a pre-specified effect size.

Specific Aims: Aim 1: To identify a preferred therapy between **cryotherapy**, **compression** therapy, or **placebo** at prevention of patient reported CIPN symptoms after 12 weeks of therapy. We will define success as a change in the FACT NTX of <5 points from baseline to 12-week evaluation. *We expect that either cryotherapy or compression therapy will be selected as the most promising therapy, meaning fewer subjects in these arms will have CIPN patient reported symptoms at 12 weeks compared to the placebo arm.* Aim 2: To evaluate the effect of **cryotherapy, compression** therapy, and **placebo** on objective sensory and motor functional tests. We will estimate changes from baseline to 12-weeks with the tuning fork, Neuropen, timed get up and go test, and tandem/unipedal stance test. *We expect that subjects treated with either cryotherapy or compression therapy will have less change in objective sensory and motor functional tests compared to placebo.*

Results and Significance: To date we have accrued 61 patients; median age 55 (range 28-82). The study population is racially and ethnically diverse; 16 patients are White (26.2%); 15 are Black (24.6%), and 9.8% are Asian; 21 are Non-Hispanic (36.1%) and 26 are Hispanic (41.6%). After analysis of 45 patients, the stopping role was not met which resulted in continuation of enrollment.
CIPN can be a devastating long-term complication of ESBC treatment affecting patients' quality of life and function long after treatment ends. To date we have not been successful at preventing or treating CIPN. These results will also inform a large prospective randomized trial within the SWOG network in hopes of identifying a non-pharmacologic, low-cost, readily available intervention aimed at CIPN prevention and could bring us one step closer to improving the lives of cancer survivors.

Poster 2. - Session 1: May 24, 1:45pm

Intra-Individual Pain Variability and Phenotypes of Pain in Sickle Cell Disease: A Secondary Analysis from the Pain in Sickle Cell Disease Epidemiology Study (PiSCES)

Authors: Nitya Bakshi, MBBS, MS [1,2], Scott Gillespie, MS, MSPH[4], Donna McClish, PhD[3] , Courtney McCracken, PhD[4], Wally R. Smith, MD[3], and Lakshmanan Krishnamurti, MD[1,2]

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Objective: The objective of this study was to determine impact of day-to-day intra-individual pain variability on patient outcomes in sickle cell disease (SCD), in PiSCES, the largest epidemiological study of pain in SCD.

Specific Aims:
Aim 1: Determine the association of intra-individual pain variability with patient outcomes and psychological factors in PiSCES.
Aim 2: Identify phenotypes or sub-groups of SCD pain, based on measures of pain intensity and intra-individual pain variability, in PiSCES.

Background: Painful vasocclusive episodes are the hallmark of SCD, a chronic multi-system disorder, which affects about 100,000 individuals in the United States and disproportionately impacts minorities and those of lower socioeconomic status. Pain is a major cause of morbidity, and poor health-related quality of life (HRQoL) in SCD, and about one-third of adults with SCD experience daily or near daily pain. There are wide inter-individual differences in the pain experience, and mean pain intensity alone is insufficient to describe pain phenotypes in SCD.
PiSCES collected daily pain diaries from adults with SCD for a 6-month period. We calculated metrics of intra-individual pain variability and mean pain intensity for 139 participants with <10% missing daily pain intensity data in the first 28-days of the study. Missing pain intensity scores were imputed by the last observation carry-forward method, for up to 2 missing days. We assessed multiple facets of pain variability: 1) *amplitude*, measured by the standard deviation, 2) *temporal dependency*, measured by the first-order autocorrelation, and 3) *temporal instability*, measured by the mean square of successive differences, and the day-to day probability of acute change in pain. We performed Spearman rank correlations between measures of intra-individual pain variability and outcomes. We then used k-means clustering to identify phenotypes of pain.

Results and Significance: We found that pain variability was inversely correlated with HRQoL, except in those with daily or near daily pain. Pain variability was positively correlated with affective coping, catastrophizing, somatic symptom burden, sickle cell stress, healthcare utilization and opioid use.
We found 3 sub-groups or clusters of pain phenotypes in SCD. ***Cluster 1*** included individuals with low mean pain, low pain variability, and lowest proportion of pain days and opioid use. Individuals in Cluster 1 tended to be younger and have the best HRQoL scores, along with lower levels of catastrophizing, stress and use of affective coping strategies. Cluster 1 most

consistently differentiated itself from clusters 2 and 3 on subscales of HRQoL and psychological factors. ***Cluster 2*** included individuals with the highest levels of mean pain, highest temporal dependency, and highest proportion of days with pain and opioid use. ***Cluster 3*** included individuals with high levels of mean pain, highest temporal instability, but with lower temporal dependency, proportion of days with pain and opioid use when compared to cluster 2. Differences between cluster 2 and 3 were limited to physical function and social function with cluster 3 having higher median scores as compared to cluster 2 on these subscales, but individuals in cluster 3 were younger than individuals in cluster 2. Psychological characteristics were similar between cluster 2 and 3, but different from cluster 1. The proportion of days with opioid use was different across all 3 clusters, with cluster 2 having the highest proportion of days with opioid use, despite having lower proportion of days with crisis as compared to cluster 3. There was no difference in median number of SCD comorbidities, or proportion of patients with avascular necrosis between the 3 clusters.
We conclude that intra-individual pain variability is associated with patient outcomes and psychological characteristics in SCD, and is useful in delineating phenotypes of pain in SCD.

Poster 3. - Session 1: May 24, 1:45pm

Altered Excitatory to Inhibitory Neurochemical Ratio in the Left Dorsolateral Prefrontal Cortex is Associated with Pain and Resting-State Functional Connectivity in Fibromyalgia Syndrome

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Objective: The objectives of this study were to establish whether excitatory and inhibitory neurochemical concentrations are altered in the top-down pain processing neural circuitry such as the left dorsolateral prefrontal cortex (L-DLPFC) and define the relationship between metabolic dysfunction, functional connectivity, and acute and clinical pain measures.

Specific Aim(s): The primary aim of this study was to determine whether baseline excitatory-to-inhibitory (E/I; Glutamate/GABA) neurochemical concentrations in the L-DLPFC are altered in participants with FMS compared to healthy pain-free controls using ^{1}H-MRS. Secondly, we aimed to determine the relationship between E/I concentrations, acute and clinical pain sensitivity, and resting-state functional connectivity in participants with fibromyalgia syndrome. We hypothesized that the Excitatory/Inhibitory (E/I) ratio within the L-DLPFC would be altered in participants with fibromyalgia compared to pain-free controls and, secondly, within the chronic pain cohort, that E/I ratio would be associated with both acute thermal pain thresholds and tolerances.

Background: The central mechanisms underlying Fibromyalgia syndrome remain undetermined; however, there is increasing evidence to suggest that neurochemical imbalances may play a critical role in the pathophysiology of the condition. The DLPFC is a heterogeneous cortical structure involved in cognitive, affective, and sensory processing of pain known to mediate top-down pain modulation. Increased glial reactivity and GABA receptor upregulation have been identified as potential CNS generators of pain chronicity which could contribute to, or be facilitated by, metabolic imbalances. Direct evidence of dysfunction in excitatory and inhibitory (E/I) neurotransmitter concentration and their relationship to pain sensitivity in cognitive circuitry such as the DLPFC have not yet been shown. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive imaging approach capable of resolving chemical concentrations *in vivo* that can be implemented to identify dysfunction in neuroanatomical regions of interest.

Results: E/I ratios in were significantly higher in people with FMS (n=51) than in healthy controls (n=16), in relation to both water (ΔM = .084, t(18.307) = 2.219, p = .039) and cr (ΔM = .085, t(18.303) = 2.241, p = .038). The fibromyalgia group was stratified to examine E/I ratio in individuals with and without depression compared to healthy controls which yielded a similar statistically significant result. In participants with fibromyalgia, E/I ratios in relation to both water and Cr significantly predicted thermal pain tolerance (R^2 = .101, F(1,49) = 5.530, β = .318, p = .023 and R^2 = .103, F(1,49) = 5.632, β = .321, p = .022, respectively). Similarly to pain tolerance, the models significantly predict thermal pain threshold (water: R^2 = .081, F(1,49) = 4.315, β = .284, p = .043; Cr: R^2 = .083, F(1,49) = 4.425, β = .288, p = .041). In the fibromyalgia cohort,

a significant positive relationship was identified between E/I ratio and the composite Brief Pain Inventory Scale as well as the resting state functional connectivity between the L-DLPFC-dACC.

Significance: We provide the first evidence of excitatory/inhibitory imbalance within the DLPFC in fibromyalgia syndrome, which we demonstrated to be positively associated with acute/clinical pain measures and the degree of resting-state functional connectivity to affective pain circuitry (dorsal anterior cingulate cortex). Together these results suggest a dysregulation of excitation and inhibition in top-down pain modulatory networks with potential pathophysiological implications in pain processing. Furthermore, this evidence provides potential pharmacological and neuromodulatory therapeutic targets for the treatment of fibromyalgia syndrome.

Poster 4. – Mitchell Max Awardee – Presentation May 25 – 12:25pm

Stress Exacerbates Orofacial Pain to a Greater Degree in Female Rats

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Background: Approximately 20% of the U.S. population suffers from chronic pain, and certain pain conditions in the orofacial region are more prevalent in women. However, there is a limited understanding of why orofacial pain conditions disproportionately affect women. Clinical studies indicate that psychological stress is a contributing factor in the etiology of orofacial pain disorders. Despite this prevalence, the limited research on the effects of stress on orofacial inflammatory pain is reported exclusively in male rodents. A single study in both male and female rats indicates that restraint stress enhances mechanical orofacial allodynia to a greater degree in females during a model of infraorbital neuropathic pain. It remains unclear whether stress-induced exacerbation of orofacial pain occurs in female rodents. Possible mechanisms involved in stress exacerbated orofacial pain may involve the astrocytes, which are known to have a neuroprotective and neurotoxic effect in the brain and spinal cord. Studies have indicated that restraint stress decreases Glial Fibrillary Acid Protein in the brain (GFAP), while other studies have shown that astrocytes significantly increase 1 day after exposure to Complete Freund's Adjuvant (CFA; inflammatory agent) into the masseter muscle. However, the role of astrocytes in stress exacerbated orofacial pain in trigeminal pain pathways, and whether these glial cells are involved in stress exacerbated orofacial pain in females remains unclear. An undetected sexually dimorphic effect of stress on orofacial pain may be one factor underlying the greater prevalence of orofacial pain disorders in women.

Specific aim(s): In this study we examined (1) the role of sub-chronic stress (forced swim test; FST) on inflammatory orofacial mechanical allodynia in female compared to male rats and correlated pain behaviors to (2) plasma corticosterone levels, and (3) astrocyte expression in the trigeminal nucleus caudalis (TNC) and parabrachial nucleus (PBN). We hypothesized that sub-chronic stress evokes greater orofacial pain behaviors and glial activity in the ascending trigeminal pain pathway in female rats.

Results and Significance: Here, we report that CFA (30 µL) injection into the right vibrissal pad evoked significant and comparable mechanical allodynia in both male and female rats. FST evoked a significant and comparable increase in the percentage of time spent immobile. However, females developed greater and longer-lasting orofacial mechanical allodynia one, four, and eight days post-FST. Orofacial pain behaviors returned to normal on day 11, as did corticosterone levels. Also, our preliminary data indicate that inflamed males exposed to the FST express more GFAP in the PBN when compared to sham. On the other hand, female PBN expressed comparable GFAP after exposure to FST or sham conditions, indicating a potential sex dimorphism in astrocyte expression that may be contributing to sex differences during stress exacerbated orofacial pain.
Conclusions: Our data indicate that there are sex differences in the effects of sub-chronic stress on orofacial pain. Understanding the influence of stress on orofacial pain and the role of glial cells is vital to understanding why orofacial pain conditions are more common in women.

Poster 5. - Session 1: May 24, 1:45pm

Pilot Study of Absolute Telomere Length in Preterm Infants

Sharon G. Casavant, PhD, RN; Hongfei Li, BS; Bo Reese, PhD; Xiaomei Cong, PhD, RN

Objectives: The objective of this pilot study was to describe absolute telomere length in a sample of preterm infants at NICU discharge.

Specific Aims: Examine associations between repeated painful/stressful procedures or treatments, feeding types, infant demographics, antibiotic use and altered telomere length at NICU discharge using buccal swabs and quantitative polymerase chain reaction (qPCR) with preterm infant neurodevelopmental outcomes.

Background: Annually, ~15 million babies are born preterm (<37 weeks' gestational age globally. In the neonatal intensive care unit (NICU) environment, infants are exposed to repeated stressful or painful procedures as part of routine life-saving care. These procedures have been associated with epigenetic alterations that may lead to increased risk of neurodevelopmental disorders. Telomere length has been negatively associated with adverse life experiences in

Results: Among our preterm infant samples, the mean absolute telomere length was far greater than the average adult telomere lengths. While there were no statistically significant associations found between absolute telomere length and pain, feeding method and neurodevelopment, a trend between sex was noted where male telomere lengths were shorter than females as they aged. Additional buccal samples are currently being collected in a NICU follow-up clinic to examine.

Significance This is the first study in the United States with a sample size greater than 10 and one of four globally to evaluate preterm infant telomere length. While the other studies used relative telomere length, we used the more accurate absolute telomere length. We did find a trend toward sex differentiation with shorter telomere lengths among males than females. Additional large scale, longitudinal studies are needed to better identify the predictors of telomere length at the time of NICU discharge.

Poster 6. - Session 1: May 24, 1:45pm

Central Nervous System Pain Amplification in Lumbar Failed Back Surgery Syndrome

Andrea L. Chadwick, MD, MSc, FASA; Daniel J. Clauw, MD

Background: Lumbar spine pain is the most common reason for which patients visit their doctor. Although the majority of lumbar spine pain patients can be managed with conservative therapy, there are millions of individuals who undergo lumbar spine surgery for refractory pain. A challenging sequelae for these patients is the failure to derive pain relief despite the surgical intervention. Lumbar failed back surgery syndrome (FBSS)is one of the most under-studied post-surgical pain syndromes. Individuals who fail to get meaningful relief of pain after surgery have been shown to share commonalities in how their central nervous systems(CNS)process and modulate nociceptive stimuli -known as CNS pain amplification or centralized pain-that can predispose them towards developing chronic pain after surgery. Objective: The goal of the research study is to use multiple rigorous research methods to establish that patients who fail to derive pain relief from lumbar spine surgery(LSS) exhibit phenotypic and physiologic evidence of CNS amplification and centralized pain.

Specific Aims: Aim 1: To demonstrate that common patient characteristics consistent with a centralized pain phenotype are associated with a patient's failure to derive benefit from LSS.
Aim 2: To confirm that altered pain processing mechanisms consistent with centralized pain are seen in patients who have failed to respond to LSS. To test Aims 1 and 2, a prospective, observational study will recruit 100men and women with chronic low back pain(cLBP)who are scheduled to undergo LSS. Patient phenotyping via patient reported outcomes (PROs) and quantitative sensory testing (QST) procedures will take place in one visit pre-operatively. At six months post-surgery, we will administer two questionnaires to determine analgesic response to surgery. Phenotyping and QST will also be done in a cross-sectional manneron50age and sex-matched healthy controls (HC) and50age and sex-matched patients with an established diagnosis of FBSS. Results and Significance: Preliminary analysis of pain phenotyping of the enrolled FBSS (n=22) and HC(n=30) participants of the K23study has been performed. Results indicate that FBSS patients

show higher levels of centralized pain and50% of them meet diagnostic criteria for being FM-positive. Furthermore, other traits consistent with CNS pain amplification include a significantly higher PainDETECT score and increased depression, anxiety, sleep problems, and fatigue. Analysis of preliminary physiologic data including pressure pain thresholds, temporal summation, and cuff algometry do not show significant differences between groups however, FBSS patients exhibit increased temporal summation compared to HCs, which was trending towards statistical significance (p=0.06). We have successfully completed data collection on 20 patients having LSS with follow up to 6-months. Preliminary interim analysis shows that at baseline prior to surgical intervention, LSS patients have mean worst NRS pain scores of 5.7, have moderate levels of neuropathic pain (PainDETECT mean score of 14.4), and 13% were taking opioids. With regards to centralized pain measures at baseline, the mean FMness score prior to surgical intervention was 9.9 and 18% met diagnostic criteria for being FM-positive, which is a higher proportion than what has been seen in line with what has been seen pre-operatively in other surgeries such as knee and hip arthroplasties (6.2%)39. In order to deduce successful vs non-successful analgesic outcome for surgery, we define a positive or successful analgesic outcome from this surgery as greater than 50% reduction in worst pain NRS at 6-monthscompared to baseline. With this definition, our initial analysis is showing that 65% of patients are not achieving substantial relief from surgery and as such meet criteria for FBSS.

Poster 7. - Session 1: May 24, 1:45pm

Outcomes of Operative and Nonoperative Management of Meniscal Tear

Jamie E Collins, PhD
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Objective: To investigate the association between treatment outcomes and socioeconomic and demographic characteristics in a randomized control trial (RCT) of physical therapy (PT) vs. surgery in participants with meniscal tear and osteoarthritis (OA).

Specific Aims: Aim 1: To describe outcomes of treatment for meniscal tear in OA, including pain and total knee replacement (TKR). Aim 2: To evaluate the association between baseline socioeconomic and demographic characteristics and treatment outcomes.

Background: Knee pain in the setting of meniscal tear and OA is common in middle-aged and older adults. Relatively little is known about the effects of treatment on longer term(>2 year)outcomes, or about the associations between treatment outcomes and socioeconomic and demographic factors. We used data from the MeTeOR Trial, a multi-centered RCTof arthroscopic partial meniscectomy (APM) with PT vs. PT alone in patients with degenerative meniscal tear, knee symptoms, and mild-to-moderate knee OA. Participants eligible for the trial were 45 years or older, had knee pain of at least four weeks duration, and had evidence of degenerative meniscal tear and OA on imaging. Participants assigned to the PT arm were permitted to cross over to undergo APM, thus we considered both intention-to-treat (ITT) and as-treated analyses. Participants completed questionnaires prior to randomization, at 3 and 6 months post-randomization, and every 6 months thereafter through 60 months. Knee pain was assessed with the Knee Injury and Osteoarthritis Outcome Score (KOOS) pain scale. We also evaluated the incidence of total knee replacement (TKR)in the index knee. We utilized piecewise linear regression models to assess the association between treatment group, baseline factors, and longitudinal pain.

Results and Significance: Three hundred fifty-one participants were randomized to undergo APM(n = 174) or PT(n = 177). Ten subjects randomized to APM did not undergo surgery and sixty-eight randomized to PT crossed over to APM, for as-treated samples of 232 in the APM group and 119 in the PT group. The average age was 58, 57% female, average BMI 30. Eighty-four percent of the cohort was white, 10% Black, 2% Hispanic, and 1% Asian. The average (standard deviation (SD)) KOOS pain at baseline was 46.9 (16.1). The mean (SD) improvement in KOOS pain over 3 months was20 (18). Overall improvementthrough5 years was 29(19). Twenty-five participants underwent TKR over 5 years. ITT and as-treated analyses demonstrated similar results: APM was associated with slightly better KOOS pain scores at three months post-randomization of approximately 5 points. There were not statistically or clinically significant differences between the groups at any subsequent time points. Black participants had significantly higher baseline KOOS pain compared to white participants (mean difference 8.5, 95% confidence interval (CI):(3, 14).By 5 years post-randomization

scores were similar between the groups (mean difference 4.5, 95% CI: (-2.9, 11.9)). Twenty-three (8%) white participants underwent TKR over five years, compared to 1 (3%) Black participant. College graduates had lower baseline pain compared to participants with some college or high school educations. By twenty-four months, participants with some college and college graduates achieved similar pain levels, while subjects with a high school education had average pain scores approximately six points higher than the other two groups; by 5 years this difference was approximately 10 points. Number of co-morbidities was not associated with baseline or improvements in KOOS pain. Neither education nor comorbidities were associated with TKR incidence. Socioeconomic and demographic characteristics were associated with different baseline pain levels and improvements in pain over 5 years in an RCT of surgical vs. non-operative therapy for meniscal tear and OA. Future work will consider heterogeneity of treatment effect by these characteristics.

Poster 8. - Session 1: May 24, 1:45pm

Multisensory hypersensitivity in persistent post-traumatic headache is associated with higher disease burden.

Melissa M. Cortez[1], Leah Millsap[1,2], K.C. Brennan[1]

OBJECTIVE: To examine quantitative sensory symptoms and psychophysical discomfort thresholds to light and mechanical touch within post-traumatic headache (PTH)subjects, compared to non-headache healthy control subjects.

SPECIFIC AIMS:1) Determine whether psychophysical sensory sensitivity thresholds are lower in PTH subjects compared to controls. 2) Evaluate the relationship between sensory thresholds and headache burden.

BACKGROUND: Symptoms of increased light and tactile sensitivity (photophobia and allodynia) and signs of altered sensory function have been reported in PTH, and have been associated with a higher likelihood of persistent post-injury. These observations have led to the hypothesis that PTH is generated by a combination of cranial, peripheral and central sensitization, which is corroborated by preclinical TBI models implicating sensitization of trigeminal and somatosensory pathways as pain generators. Importantly, sensory dysfunction may also herald more severe disease, and could serve as treatment targets in those with the greatest disease burdens.

RESULTSAND SIGNFICANCE: We tested light and tactile sensitivity, along with measures of disease burden, in 30 persistent PTH subjects and 35 controls. Headache duration since injury ranged from 3 months to 15 years. Seventy-nine percent of PTH subjects exhibited interictal sensory hypersensitivity based on psychophysical assessment. Of those exhibiting hypersensitivity, 54% exhibited both light and tactile sensitivity. Median light sensitivity thresholds were significantly lower in persistent PTH subjects, compared to controls (p=.0006). The significant difference in light sensitivity thresholds between the PTH and control groups remained significant after regression analysis controlling for GAD and PHQ (p = .0003). Sixty percent of persistent PTH subjects had allodynia overall; 52% had facial allodynia and 60% had forearm allodynia. Periorbital and forearm median tactile pain thresholds were significantly lower in persistent PTH compared to controls (p=.01 and .003 respectively). Again, differences in VFH thresholds between the PTH and control groups remained significant after regression analysis controlling for GAD and PHQ (Peri-orbital site, p = .0008; Forearm, p = .02).
Cortez, 2Low light sensitivity thresholds were positively correlated with low VFH thresholds in persistent PTH subjects, which was statistically significant at the forearm site, an extracephalic site (forearm, rho 0.52, p=.004; periorbital, rho 0.28, p=.09). Low light sensitivity thresholds were associated with ictal sensory symptom scores, though only photophobia related scores reached statistical significance (SF-PhotoQ scores, rho -0.34. p=.04; ASC-12 scores, rho -0.30, p=.07).Finally, PTH subjects with both light and tactile sensitivity had significantly higher headache frequencies and lower sensitivity thresholds to both modalities, compared to those with single or no sensory hypersensitivity. The observed patterns suggest that hypersensitivity across multiple modalities may be functionally synergistic and reflect a higher disease burden. Of note, the pattern of sensory amplification seen in our sample of PTH subjects differed from published patterns in chronic migraine, demonstrating a more prominent pattern of extracranial sensitization. In summary, we show evidence of multisensory dysfunction in greater than 50% of persistent PTH subjects. We also show that light and tactile sensitivity not only correlate with each other, but appear to be functionally synergistic, in that having both sensory amplifications was associated with the highest headache attack frequencies, greatest ictal sensory symptom burden, and lowest sensory thresholds overall. The correlated, apparently additive nature of sensory amplifications, and their scaling with measures of disease severity, make it appealing to hypothesize that a central

process is involved and prompt further pathophysiological investigation into the underpinnings of this multisensory gain in PTH. On a clinical basis, the correlation of multisensory dysfunction with attack/disease severity also suggests the use of sensory amplifications as potential markers of disease, risk of chronification, and treatment response.

Poster 9 - Session 1: May 24, 1:45pm

Effects of combined and alone transcranial motor cortex stimulation and mirror therapy in phantom limb pain: A randomized factorial trial

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Objective: The objective of this clinical trial is to test the effects of transcranial direct current stimulation (tDCS) in the motor cortex and mirror therapy (MT) in patients with traumatic lower limb amputation; and whether the motor cortex plasticity changes drive these results.

Specific aims: We aimed to test in a factorial trial whether tDCS combined with MT has a greater impact on PLP than any therapy alone in traumatic lower limb amputees. Second, we tested the effects of these interventions on motor cortex plasticity, by assessing cortical excitability and cortical mapping changes before and after treatment using transcranial magnetic stimulation (TMS). Lastly, we tested whether changes in motor cortex plasticity (paired-pulse TMS and mapping) were correlated with PLP changes.

Background: Phantom limb pain (PLP) is a frequent complication in amputees, which is often refractory to treatments. In PLP, maladaptive plasticity associated with sensory deafferentation following an amputation is one of the contributors to excessive pain. In this context, a potential neural target to modulate the dysfunctional sensorimotor circuits is the primary motor cortex (M1). We hypothesize that combined M1 tDCS and MT would induce larger PLP relief as compared with any therapy alone and no therapy. These effects would be driven by inducing greater cortical excitability modulation, specifically by increasing intracortical inhibition and facilitation and leading to changes over motor cortex mapping.

Methods: In this large randomized, double-blinded, two-site, sham-controlled, 2x2 factorial trial, 112 participants with traumatic lower limb amputation were randomized into treatment groups (Figure 1). The interventions were active or covered MT for four weeks (20 sessions, 15 mins each) combined with two weeks of either active or sham tDCS (10 sessions, 20 mins each) applied to the contralateral primary motor cortex. The primary outcome was PLP changes on the visual analogue scale at the end of interventions (four weeks). Motor cortex excitability and cortical mapping were assessed by transcranial magnetic stimulation (TMS).

Results and Significance: We found no interaction between tDCS and MT groups (F=1.90, p=0.13). All groups reported analgesic effects. In the adjusted models, there was a main effect of active tDCS compared to sham tDCS (beta coefficient=-0.99, p=0.04) on phantom pain. The overall effect size was 1.19 (95% CI: 0.90, 1.47). No changes in depression and anxiety were found. We found no difference at follow-up. TDCS intervention was associated with increased intracortical inhibition (coefficient=0.96, p=0.02) and facilitation (coefficient=2.03, p=0.03) as well as a posterolateral shift of the center of gravity in the affected hemisphere. MT induced no motor cortex plasticity changes

assessed by TMS. We found a short-term statistically significant and clinically important PLP reduction by motor cortex tDCS. These findings indicate that transcranial motor cortex stimulation might be an affordable and beneficial PLP treatment modality.

Poster 10. - Session 1: May 24, 1:45pm

Spinal 12/15-Lipoxygenase activation contributes to NSAID-unresponsive pain hypersensitivity

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Objective: The current study examines the role of the 12/15-Lipoxygenase enzyme 15-LOX-1 and its metabolites (12/15-LMs) in the acute to chronic transition phase of pain hypersensitivity in rodents.

Background: While opioids produce moderate relief of chronic Rheumatoid Arthritis (RA) and neuropathic pain, they can impart serious risks including addiction with long-term use. Current non-opioid therapies (steroids, biologics, NSAIDs) alleviate clinical signs of arthritis, yet joint pain is often unremitted in RA patients; thus, novel analgesics are critical. The chronic neuropathic-like pain state in RA results from peripheral and central sensitization, persisting after inflammation resolution. In the K/BxN mouse model of RA, this post-inflammatory allodynia is Toll-like Receptor 4 (TLR4)-dependent and is attenuated by opioids as well as transiently reduced by gabapentin yet is unresponsive to NSAIDs. The acute to chronic pain transition is modeled in part by spinal (intrathecal, IT) delivery of the TLR4 agonist, lipopolysaccharide (LPS), at least in males. The resulting pain hypersensitivity is unchanged by the NSAID ketorolac administered at analgesic doses inhibiting spinal PGE_2 release.

Results: In addition to the expected IT LPS-induced increases in cyclooxygenase activity, we observe significantly elevated levels of 12/15-LMs in lumbar spinal cord and primary spinal microglia, concurrent with microglial upregulation of 15-LOX-1 and expression of allodynia in male rats. Pretreatment with the *in vivo* active, CNS-permeant molecule ML351, which selectively inhibits 15-LOX-1, reduces activity of 15-LOX-1 overexpressed in HEK-293T cells and abrogates IT LPS-induced pain hypersensitivity in male rodents. Levels of spinal 12/15-LMs also are elevated in males during the acute to chronic pain transition phase of the K/BxN model of RA. This work is being extended to also include females. In addition, high-throughput screening of 15(S)-HETE in primary and secondary functional assays reveals a GPCR target enriched in nociceptors.

Conclusions: Taken together, these findings suggest that spinal TLR4-mediated allodynia is mediated by activation of microglial 15-LOX-1 in males and that IT LPS recapitulates some features of pain chronification in rodent models of post-inflammatory, neuropathic-like arthritic pain states. Ongoing studies will address the role of spinal 15-LOX-1 and downstream receptors activated by 12/15-LMs in K/BxN arthritis-induced chronic pain hypersensitivity in both males and females.

Poster 11. - Session 1: May 24, 1:45pm

Association between Underrepresented Racial or Ethnic Groups and Pain Trajectories in Breast Cancer Patients

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Objective: To understand pain trajectories in underrepresented racial/ethnic groups of breast cancer patients.

Specific Aims: Aim 1. To identify pain trajectory patterns in patients with breast cancer. Aim 2. To explore underrepresented racial or ethnic group disparities in the pain trajectories.

Background: Despite being one of the most common cancers, disparities have been shown in breast cancer screening, treatment, and outcomes. Approximately 20% to 30% of breast cancer patients reported different levels of pain1. Somewhat contradictory evidence suggests minority breast cancer patients might experience worse pain or inadequate pain treatment.2-4Pain trajectories represent pain scores over time and characterize the pain experience in an observation period.5Little is known about racial disparity in pain trajectories in breast cancer patients. This project aimed to address that knowledge gap.

Results and Significance: Secondary data analysis was conducted on electronic health record (EHR) data between Dec 2010 and May 2019 from a single medical center. The study included 1740 adult inpatients (age ≥18 years) with breast cancer. Pain scores for two years since the first breast cancer admission were used for identifying patterns of pain trajectory using group-based trajectory modeling (GBTM).6Pain was scored with a numeric rating scale (0=no pain to 10=worst pain). Multinomial logistic regression modeled the relationship between ethnicity (Hispanic vs. non-Hispanic) and race (non-White vs. White) and pain trajectory patterns, with age and cancer stage (0 to 4) as covariates. The mean age was 57.8 years (SD=12.7, range =20.9–96.7). Most of the sample were female (99.2%), cancer stage ≤ 2 (79.7%), non-Hispanic (94.2%), and White (90.3%). The detailed racial breakdown was: 2% (n = 34) Asian, 1% (n = 18) Native Hawaiian and Other Pacific Islander, 1% (n = 17) American Indian, 0.5% (n = 8) Black, and 5.3% (n = 92) other or more than one race. Four pain trajectory patterns were identified: stable/consistent very mild pain(79.0%), increasing from mild to moderate pain(8.4%), decreasing from mild to very mild pain (7.8%), and consistent moderate pain(4.7%). Racial disparity was observed in the pain trajectories at this center. The multinomiallogistic regression analysis compared other trajectories to the stable/consistent very mild pain pattern. For increasing from mild to moderate pain trajectories, age (OR:2.56, 95% CI: 1.30 –5.02, p= .025) and stage (OR:1.23, 95% CI: 1.04 –1.46, p = .016) were significant predictors. For the trajectory decreasing from mild to very mild pain, cancer stage (OR:1.46, 95% CI: 1.24 –1.73, p<.001) was the only significant predictor. For consistent moderate pain trajectory, cancer stage (OR:1.54, 95% CI: 1.25 –1.90, p<.001) was significantly predictive; in addition, non-White patients were 2.56 times more likely to have consistent moderate pain than White counterparts (OR:2.56, 95% CI:1.30 –5.02, p = .005). Ethnicity was not a significant predictor for any of the trajectory patterns. Being aware of disparities will help clinicians care for patients with complex cancer pain. Further study will explore possible mechanisms, such as the use of pain medication or pain control types. Healthcare disparities could be worse during public health emergencies such as a pandemic,7and exploring pain trajectory patterns during the pandemic period could help to understand disparities in cancer pain across racial or ethnic groups.

Poster 12. - Session 2: May 24 – 4:25pm

Subjective measures of physical function, pain behavior, and pain interference are more strongly correlated to perceived back disability than objective measures of mobility, strength, and pain sensitivity.

Authors: Nicholas V. Karayannis, MPT, PhD; Laurel Stell, PhD; Matthew Smuck, MD; James J. Gross, PhD; Christine Law, PhD; Beth Darnall, PhD; Sean C. Mackey, MD, PhD; Julia Hush, PhD

Objective: To examine the relationship between perceived back-related disability with self-reported physical function and pain-specific psychological factors, and examiner-recorded physical capacity and sensitivity measures in a cross-sectional study of 328 individuals with chronic low back pain (CLBP).

Specific aims: (1) To characterize the relationship between a subjective measures of back disability, physical health, and pain-specific psychological factors with objective measures of physical capacity and sensitivity. (2) To characterize the relationship of subjective measures with one another. (3) To characterize the relationship of objective measures with one another.

Background: The relationship between perceived disability with subjective physical health measures and objective measures of back-related function are not well understood. Addressing this knowledge gap may inform the

development of effective interventions. Relationships within and across domains were tested with Spearman correlations. Self-reported measures included PROMIS measures of Physical Function, Pain Behavior, and Pain Interference; Roland Morris Disability Questionnaire (RMDQ); Fear-Avoidance Beliefs Questionnaire, Pain Catastrophising Scale, and Chronic Pain Acceptance Questionnaire (CPAQ). Objective measures included walking speed and endurance, lower extremity functional strength, lumbopelvic range of motion and trunk endurance, and lumbar pressure-pain threshold.

Results: Perceived back disability (RMDQ) was strongly correlated with PROMIS physical function (ρ = -0.56), pain behavior (ρ = 0.51), and pain interference (ρ = 0.49); and moderately correlated with pain catastrophising (ρ = 0.37) and fear-avoidance beliefs (ρ = 0.33). RMDQ was not correlated with pain acceptance nor with any of the physical capacity and sensitivity measures. PROMIS Physical Function was only weakly correlated with walking speed (ρ = 0.26, 2-minute walk) and lower extremity strength (ρ = -0.29, 5x sit-to-stand).

Significance: An individual's perception of their back disability and physical function is most strongly characterized with pain behavior and pain interference. Lower extremity strength and walking speed were the only objective biomarkers that were weakly associated with subjective physical function. The most commonly recommended core outcome measure for clinical trials and clinical practice guideline-based care in CLBP are self-report instruments such as the Roland Morris Disability Questionnaire (RMDQ) and the Oswestry Disability Index. While self-report measures of disability are pragmatic, if used in isolation they are unlikely to capture a comprehensive view of physical function or pain-specific psychological factors that can interact with disability.

Poster 13. - Session 2: May 24 – 4:25pm

Chronic Pain Diagnosis and Treatment in Torture Survivors

Gunisha Kaur, MD, MA

An estimated 87% (27 million people) of torture survivors suffer from chronic somatic pain, such as brachial plexopathy from suspension by upper extremities or lumbosacral plexus injury from leg hyperextension. The United Nations Istanbul Protocol (UNIP) is the global standard used by all providers for the medical assessment of torture survivors, often used in conjunction with validated screens for posttraumatic stress disorder (PTSD) and major depression (MD). While the protocol provides recommendations on assessing pain in torture survivors, these guidelines are challenging to operationalize, and providers likely fail to diagnose pain in the vast majority of patients. The complexity in their clinical presentation results most frequently in pain being confounded or eclipsed by psychiatric illnesses such as PTSD, MD, or somatization. Our central hypothesis, based on strong preliminary data from 25 participants, is that the novel application in torture survivors of a validated pain screen, the Brief Pain Inventory Short Form (BPISF), can supplement the UNIP and improve its sensitivity for pain from 15% to 90%, as compared to the gold standard (a pain specialist). We will test this hypothesis with 100 participants enrolled from four human rights centers in this prospective, blind comparison to gold standard study. Objective. The objective of this study is to improve the diagnosis and treatment of chronic pain in torture survivors.

Specific Aim(s).
Aim 1. Compare the diagnosis of chronic pain in torture survivors using the standard United Nations Istanbul Protocol (UNIP) versus the UNIP plus the BPISF.
Aim 2. Evaluate the acceptability of somatic pain treatment using qualitative interviews of torture survivors.
Aim 3. Assess the feasibility of recruiting and retaining subjects in our somatic pain treatment, to inform the design of a subsequent clinical trial.

Background.
The World Medical Association (WMA) Declaration of Tokyo defines torture as the "deliberate, systematic or wanton infliction of physical or mental suffering by one or more persons acting alone or on the orders of any authority, to force another person to yield information, to make a confession, or for any other reason." Individuals are persecuted for a variety of reasons such as political opinion, ethnic background, or gender. Perpetrators of violence include government officials, police and military personnel, and highly organized gangs.

Torture survivors experience concurrent physical and psychological trauma that is sustained. Upon fleeing their home country, torture survivors often experience loss of social status, financial difficulty, and migration trauma. On arrival to host country, they may be separated from their children, be forced into detention, experience homelessness, and/or lack access to medical care. As a result of these dual traumatic experiences of persecution and complex emigration, torture survivors suffer a combination of psychological trauma and physical pain, superimposed on their chronic medical conditions. An estimated 31% of refugees suffer either posttraumatic stress disorder (PTSD) or major depression (MD). Similarly, limited studies demonstrate a high prevalence of chronic pain, as great as 87%. This pain not only persists decades after trauma, it worsens and causes increased disability. Specific types of torture are associated with specific pain sequelae. Falanga results in chronic pain, compensated gait, and peripheral neuropathy, suspension from upper extremities is associated with brachial plexopathy, and leg hyperextension is correlated with lumbosacral plexus injuries. Evaluators do not have adequate diagnostic tools to assess complex pain in torture survivors, limiting treatment and rehabilitation. Despite the estimated high prevalence of chronic pain, pain specialist physicians, like psychiatrists, are limited in number and accessibility and cannot conduct evaluations on all patients. This signifies the importance of screens, such as those applied for PTSD and MD.

Accurate diagnoses and treatment of pain is a critical component of rehabilitation. Studies indicate that while trauma cannot be eliminated, rehabilitation is achievable. For somatic pain reduction in the general population, strong evidence from large data analyses and rigorous trials demonstrates the value of physical therapy, non-opioid analgesic therapy, and trigger point injections. Survivors of torture are a uniquely complex patient population. What may seem like standard of care (e.g. trigger point injections) may not be acceptable to patients (e.g. individuals tortured by electrocution). Treatment approaches must be informed by the complexity of torture survivors' experiences.

To adequately rehabilitate survivors of torture both psychologically and physically, we must improve our ability to diagnose somatic pain. By increasing the accuracy of our pain diagnoses, we can deliver data-driven, targeted interventions that treat the source of the morbidity. This research has the potential to alter the evaluations of 70.8 million refugees, an estimated 27 million of whom have survived torture and experience chronic pain.

Poster 14. - Session 2: May 24 – 4:25pm

A pilot randomized controlled trial of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy (CIPN) and the interoceptive brain system

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Background: Over half of patients receiving neurotoxic taxane, platinum, or bortezomib chemotherapy experience CIPN—a dose-limiting toxicity involving pain, numbness, tingling, and cramping in the hands and feet. There are limited prophylactics and treatments for chemotherapy-induced peripheral neuropathy (CIPN) despite nearly 100 randomized controlled trials in humans. The lack of treatments for CIPN is partly because its pathophysiology is poorly understood.

Objective: This randomized pilot study explored whether home-based low-moderate intensity progressive walking and resistance exercise during neurotoxic chemotherapy ameliorates CIPN. We also began to test our innovative theory on the pathophysiology of CIPN, namely that CIPN and its treatment involves changes in the interoceptive brain system, which processes bodily sensations.

Specific aims: To assess the effects of exercise vs. nutrition education (control) on (1) CIPN symptoms (primary outcome: CIPN-20), (2) CIPN signs (tactile sensitivity in fingers and toes), (3) physical function (isokinetic leg strength), and (4) functional connectivity in the interoceptive brain system using fMRI. Patients were randomized 1:1 to exercise (home-based, low-moderate intensity, progressive walking and resistance training) or nutrition education (control) for 12 weeks

starting at their first infusion of neurotoxic chemotherapy. All outcomes were assessed at 0, 6, and 12 weeks (except MRI which was not assessed at 6 weeks).

Results and significance: Nineteen patients (65±11 years old, 52% women, 42% breast cancer, 32% gastrointestinal cancer) scheduled to receive taxane, platinum, or bortezomib chemotherapy were randomized to exercise or nutrition education control. We observed moderate to strong beneficial effects of exercise on CIPN symptoms (effect size [ES]=0.7 and 0.5 at 6 and 12 weeks), CIPN signs (ES=1.0 and 0.1), and physical function (ES=0.4 and 0.3). CIPN symptom severity was positively correlated with functional connectivity across the interoceptive brain system's sensory and awareness networks (between the posterior cingulate and thalamus, between the posterior insula and anterior insula; ES=0.3). Exercise reduced functional connectivity between the interoceptive brain system's sensory and awareness networks (between the posterior cingulate and posterior insula; ES=1.4).

In conclusion, exercise during neurotoxic chemotherapy attenuated CIPN signs and symptoms, perhaps via changes in interoceptive brain circuitry. These findings may help improve our understanding of CIPN to develop and optimize new treatments. Future work should test for replication with a larger sample.

Poster 15. - Session 2: May 24 – 4:25pm

Racism-related stress mediates the association between sleep fragmentation and reported pain sensitivity in a study of healthy non-Hispanic Black and White adults

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Objective: To determine the extent to which racism-related stress mediates the association between sleep fragmentation and pain sensitivity as well as to explore the link between racism-related stress and pain neurophysiology.

Background: Sleep and pain are robustly associated, so that greater sleep disruption is linked with greater pain prevalence, sensitivity, and interference. A previous meta-analysis of 13 studies identified stress as one putative mediator of this association. However, research in this area has principally been conducted with non-Hispanic White (NHW) participants, which limits knowledge about the generalizability of findings across racial/ethnic groups that systematically experience an additional burden of stress from experiences of racism and discrimination. Specifically, both interpersonal and structural racism pervasively impact Black individuals in the US. The scientific premise of this study is that racism-related stress – or the effect of racism on psychological wellbeing – might be a particularly important mechanism for the association between sleep and pain among Black adults living in the US sociocultural context.

Specific aim(s): The present study had two specific aims. First, we aimed to examine self-reported racism-related stress [i.e., total scores on the Index of Race-Related Stress (IRRS)] as a mediator of the association between actigraphy-derived sleep fragmentation and self-reported pain sensitivity [i.e., total scores on the Pain Sensitivity Questionnaire (PSQ)] in a sample of 51 healthy adults [NHW=24; non-Hispanic Black (NHB=27)]. Second, we aimed to explore the association between racism-related stress and mu-opioid receptor (MOR) binding potential – a positron emission tomography measure of the extent to which a selective MOR agonist binds to MORs in a given brain region – during experimental pain. Based on findings from a previous study examining discrimination and pain-related brain activity, we particularly examined MOR binding potential in the medial prefrontal cortex and ventral striatum.

Results and Significance: Consistent with previous work, NHB participants demonstrated significantly greater racism-related stress [t_{50}=6.5, p<.001, d=1.7], reported pain sensitivity [t_{50}=2.6, p=.01, d=.7], and actigraphy-derived sleep fragmentation [t_{50}=3.1, p=.003, d=.9] than NHW participants. Open-ended responses indicated that being passed over for opportunities (n=10), policing (n=3), derogatory remarks (n=2), and stereotyping (n=5) were key sources of racism-related stress. There were significant, positive correlations among all three variables, so that greater racism-related stress was associated with greater pain sensitivity (r=.37, p=.008) and sleep fragmentation (r=.33, p=.02) across the sample. Sleep fragmentation and pain were also associated across the sample (r=.28, p=.04). Racism-related stress mediated this relationship [indirect effect bootstrapped 95% CI=.0024, .041] so that for every 1-unit increase in IRRS total scores (total score possible range=0-184), there was a .01-unit increase in PSQ total scores (total score possible range=0-10). In the present study, 34% of the total effect of sleep on pain operated indirectly through racism-related stress. Racism-related

stress was also positively associated with MOR binding potential values in bilateral ventral striatum (left: r=.28, *p*=.046; right: r=.31, *p*=.028) and left (r=.30, *p*=.035), but not right (r=.25, *p*=.076), medial prefrontal cortex during experimental pain. Taken together, the present findings suggest that racism-related stress might be a mechanism by which sleep disruption and pain sensitivity are associated, particularly among NHB adults. Further, stress from experiences of racism might impact brain regions thought to be involved in the transition from acute to chronic pain. If reproduced by future work, the present results would support the development of US policies mitigating the impact of racism on Black individuals' health and wellbeing, as well as the development of individual-level interventions targeting racism-related stress to reduce the burden of pain on Black adults.

Poster 16. - Session 2: May 24 – 4:25pm

Smartphone delivered progressive muscle relaxation for the Treatment of Migraine in Primary Care

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Objective: In an effort to create evidence based, scalable, accessible forms of behavioral therapy for migraine prevention, we sought to assess the feasibility and acceptability of Progressive Muscle Relaxation (PMR) in a smartphone application (app) in the Primary Care setting.

Specific aims: 1. To assess feasibility (frequency, duration) and acceptability (satisfaction score) of the RELAXaHEAD intervention (diary plus PMR) as compared to monitored usual care (MUC) (diary only) in the Primary Care setting during a 90-day period. 2. To explore whether RELAXaHEAD as compared to MUC improved clinically meaningful migraine related outcomes as defined as a change in Migraine Disability Assessment Scale (MIDAS) scores and a reduction in headache days.

Background: Migraine afflicts over 47 million Americans and is the second most disabling condition. Healthcare utilization rates for migraine are high, with over six million ambulatory visits annually and greater than 50% of all of these visits occurring in primary care settings. One out of every ten primary care consultations is for headache, and migraine accounts for at least 75% of these headache visits. Migraine preventive treatment can consist of preventive medication and/or behavioral therapy; the best treatment is typically a combination of both. The level A evidence-based behavioral therapies for migraine are Cognitive Behavioral Therapy (CBT), biofeedback, and relaxation. However, there have been many barriers to patients with migraine receiving adequate treatment in the primary care setting, from under-diagnosis to under-treatment. In the primary care setting, there is on average a four-year delay between migraine diagnosis and the start of preventive treatment. Also, PCPs are familiar with the evidence-based behavioral treatment options but often refer to non-evidence based nonpharmacologic treatments. Physicians and patients face barriers in finding providers trained in evidence-based behavioral therapies for migraine. Effective, accessible, nonpharmacologic, prevention management strategies are needed to improve migraine management in the primary care setting. Previously published, the RELAXaHEAD smartphone application (app) was developed and beta-tested by both headache specialists and people with migraine. It contains progressive muscle relaxation (PMR), a level A evidence-based treatment for migraine prevention, and has back-end analytics to capture time spent playing PMR. A single-arm study of the feasibility of RELAXaHEAD showed that people with migraine in a tertiary care neurology practice were willing to practice PMR for up to 6 weeks, and that there may be a dose-dependent relationship in the effect of the PMR. In this study, we asked participants to use the app daily to assess adherence and declining rates of use, accepting that adherence might be modest based on prior literature.

Results and Significance: Of 139 participants (77 PMR, 62 control), 83% were female, mean age was 41.7 ± 12.8 years. Most (78%) had moderate-severe disability. Using a 1-5 Likert scale, participants found the app easy to use (mean 4.2 ± 0.7) and stated that they would be happy to do the PMR again (mean 4.3 ± 0.6). For the first 6 weeks, participants did the PMR 2-4 days/week but adherence declined thereafter. Per session duration was 11±8 minutes. When comparing weekly headache days reported during the 90 day period, there were 3 fewer in the PMR arm compared to the diary only arm (p = 0.45). Mean decrease in MIDAS score in the PMR arm was 22.8±33.3 points versus 8.7±41.4 points in the control arm (P=0.1, Cohen's d=0.38).
Smartphone delivered PMR may be an acceptable, accessible form of evidence-based therapy for migraine that can be offered in primary care. Mean effects show a small-moderate difference in the disability scores between the two groups. Preliminary results indicate a small non-significant reduction in headache days with use of the PMR.

Poster 17. - Session 2: May 24 – 4:25pm

Resilience and Pain: Understanding sources of resilience across racial groups

Authors: **Calia A. Morais[1] ,** Dottington Fullwood,[2] Shreela Palit,[1] Roger B Fillingim,[1] Michael E. Robinson[3], Emily J Bartley[1]

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Objective: To examine the role of resilience on pain-related outcomes, with the goal of understanding how different sources of resilience manifest across Non-Hispanic Black (NHB) and non-Hispanic White (NHW) older adults with chronic low back pain (cLBP).

Specific Aims: (1) Understand differences in pain severity, functioning, and sources of pain resilience across NHBs and NHWs. (2) Investigate how the relationship between sources of pain resilience and pain vary across NHBs and NHWs.

Background: Racial minorities are disproportionally affected by pain and its associated consequences of functioning. Compared to NHWs, NHBs report higher pain intensity, greater pain-related disability.While risk factors contribute to these pain disparities, little is known regarding how sources of resilience influence these differences, despite the growing body of research supporting the protective role of resilience in pain and disability among older adults with chronic pain. To address this gap, the current study sought to examine the association between psychological resilience (trait resilience, gratitude) and pain outcomes (movement-evoked pain, physical functioning), and the moderating role of race across these relationships. This is a secondary analysis of the Adaptability and Resilience in Aging Adults (ARIAA) (K99AG052642).

Results and Significance: There were 45 participants that identified as NHW and 15 participants that identified as NHB. Race was a significant correlate of pain outcomes with NHBs reporting greater movement-evoked pain (r = 0.27) than NHWs. After controlling for significant covariates (sex, age, marital status, income, education and body mass index-BMI), measures of movement-evoked pain were similar across both racial groups, F (1, 48) = 0.31, p = 0.57. Moderation analyses revealed that higher levels of gratitude (b = −1.23, p = 0.02) and trait resilience (b = −10.99, p = 0.02) were protective against movement-evoked pain in NHWs. In contrast, higher levels of gratitude were associated with lower functional performance in NHBs (b = −0.13, p =0.02). These findings highlight racial differences in the relationship between sources of resilience and pain-related outcomes among older adults with cLBP. Given the limited research on psychological resilience and pain outcomes among older adults, additional research is needed to identify how various aspects of psychological resilience impact pain and functioning across demographic groups. Doing so could increase understanding in how individuals use existing personal resources to cope with pain. Future studies should also examine the potential benefits of targeted psychosocial pain management interventions that improve resilience and ameliorate pain disparities among racial minorities.

Poster 18. - Session 2: May 24 – 4:25pm

Lack of effect of different pain-related manipulations on opioid self-administration, reinstatement of opioid seeking, and opioid choice in rats

David J Reiner, E Andrew Townsend, Javier Orihuel Menendez, Sarah V Applebey, Sarah M Claypool, Matthew L Banks, Yavin Shaham, S Stevens Negus

Rationale and Objective: Pain-related factors increase risk for opioid addiction, and pain may function as a negative reinforcer to increase opioid taking and seeking. However, experimental pain-related manipulations generally do not increase opioid self-administration in rodents. This discrepancy may reflect insufficient learning of pain-relief contingencies or confounding effects of pain-related behavioral impairments. Here we determined if pairing noxious stimuli with opioid self-administration would promote pain-related reinstatement of opioid seeking or increase opioid choice over food.

Methods: In Experiment 1, rats self-administered fentanyl in the presence or absence of repeated intraplantar capsaicin injections in distinct contexts to model context-specific exposure to cutaneous nociception. After capsaicin-free extinction in both contexts, we tested if capsaicin would reinstate fentanyl seeking. In Experiment 2, rats self-administered heroin after intraperitoneal (i.p.) lactic acid injections to model acute visceral inflammatory pain. After lactic acid-free extinction, we tested if lactic acid would reinstate heroin seeking. In Experiment 3, we tested if repeated i.p. lactic acid or intraplantar Complete Freund's Adjuvant (CFA; to model sustained inflammatory pain) would increase fentanyl choice over food.

Results: In Experiments 1-2, neither capsaicin nor lactic acid reinstated opioid seeking after extinction, and lactic acid did not increase heroin-induced reinstatement. In Experiment 3, lactic acid and CFA decreased reinforcement rate without affecting fentanyl choice.

Conclusions: Results extend the range of conditions across which pain-related manipulations fail to increase opioid seeking in rats and suggest that enhanced opioid-addiction risk in humans with chronic pain involves factors other than enhanced opioid reinforcement and relapse.

Poster 19. - Session 2: May 24 – 4:25pm

Evaluation of the Role of Macrophage Migratory Inhibitory Factor (MIF) in mediating Stem Cell Analgesia in a Model of Orofacial Pain

Ruparel Nikita B., Chang Phoebe, Ganatra Shilpa, Bayat Saeed, Chapa Brett

Background and Significance: Pain due to apical periodontitis (AP) is a common example of infection-induced pain due largely to evoked immune and nociceptor responses. While root canal therapy (RCT) has high success rates, persistent post-treatment pain can occur in up to 10-12% of patients. Moreover, there is a 19% greater risk of developing persistent post-treatment pain with daily increase in pain duration prior to receiving RCT. Interestingly, antimicrobial drugs provide little-to-no relief in patients with AP pain, suggestive of persistent nociceptive changes that are unaffected by microbial targeting. Therefore, identifying a novel non-opioid class of analgesics that can prevent the ***development*** of persistent dental pain may provide substantial clinical relevance. Stem cell-induced analgesia is an emerging therapeutic that has demonstrated profound efficacy in animals and patients experiencing neuropathic pain, osteoarthritis and migraine. However, its effectiveness and mechanisms involved in treating ***dental*** pain is unknown.

Objective: To define mechanisms mediating mesenchymal stem cell (MSC)-induced anti-allodynia in a mouse model of apical periodontitis. We evaluated the following specific aims:
Specific Aim 1: To evaluate the effect of human MSCs (i.e. human Stem Cells of Apical Papilla; hSCAP) on AP-induced mechanical allodynia *in vivo*.
Specific Aim 2: To evaluate the site of action of hSCAP-induced reversal of AP-induced mechanical allodynia *Specific Aim 3:* To evaluate the mechanism of hSCAP-induced reversal of AP-induced mechanical allodynia.

Results:

- Injection (i.v.) of human MSCs (i.e. human Stem Cells of Apical Papilla; hSCAP) reverse AP-induced mechanical allodynia in mice without altering the disease progression
- Injected hSCAP homes to periapical granulomas (peripheral sites of tooth infection, but not to the CNS, suggesting a peripheral site of action.
- After homing to periapical granulomas, hSCAP express a ***133-fold*** upregulation of macrophage migratory inhibitory factor (MIF).
- Conditioned media (CM) generated from co-cultures of hSCAP with mouse periapical granulomas (hereafter described as "primed" hSCAP) release MIF ***>5-fold*** compared to control media.
- CM from significantly attenuates capsaicin (CAP)-evoked $[Ca^{2+}]_I$ from mouse trigeminal (TG) neurons and this effect is reversed by anti-human MIF-Ab.

Collectively, these data support a ***novel*** peripheral mechanism for human MSC-induced inhibition of nociception due, at least in part, by MIF. Future studies will evaluate the mechanisms mediating MIF inhibition of TG sensory neurons using knockout of MIF in hSCAP using CRISPR-Cas9 gene editing technology, *in vivo* intraganglionic knockdown of MIF receptors in TG neurons and employing transgenic animals to conditionally knockout MIF receptors in TG sensory neurons with the goal to determine the neuronal subtypes that are targeted by MIF and contribute to the observed anti-allodynia.

Collectively, these studies have high medical significance as they define a novel ligand-receptor system for treating infection-induced pain, possibly leading to new non-opioid analgesics. Importantly, the combined use of ***human*** hSCAP in rodent models foster mechanistic research and increases translational significance.

Poster 20. - Session 3: May 25 – 11:40am

Probing the cellular basis of spinal kappa opioid receptor inhibition of pain

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While opioid analgesics that target the mu opioid receptor provide robust analgesia, their addictive properties have led to a devasting opioid use disorder epidemic in the United States, which has been further exacerbated by the COVID-19 pandemic. Kappa opioid receptor (KOR, encoded by *Oprk1*) agonists have emerged as a promising intervention in the search for nonaddictive analgesics, yet the cellular basis of KOR inhibition of pain is not entirely understood. To address this critical gap in knowledge, we recently developed a novel genetic tool – an *Oprk1-Cre* mouse line – to gain genetic access to KOR-expressing neurons. Using this tool, we have previously shown that KOR is expressed in a small subset of nociceptive peripheral sensory neurons, yet whether KOR is also expressed on spinal neurons involved in pain processing remains largely unexplored. Here, we provide the first in-depth analysis of KOR-expressing spinal neurons through a combination of genetic, behavioral, and molecular approaches. First, we showed that chemogenetic activation of *Oprk1* spinal neurons elicits spontaneous nocifensive behaviors, and potentiates behavioral responses to chemical pain, without affecting baseline nociceptive withdrawals. Next, we visualized *Oprk1* spinal neurons and discovered that *Oprk1* is expressed in local interneurons, as well as spinal projection neurons that target brainstem and thalamic structures that are critical for the supraspinal processing of pain stimuli. Finally, we used RNAscope fluorescent in situ hybridization to determine the molecular identity of *Oprk1* spinal neurons that may drive pain behaviors. We show that *Oprk1* is expressed within a heterogenous population of spinal neurons, including excitatory neurons that express the neuropeptide substance P as well as its receptor, NK1R, both of which are strongly implicated in driving pain behaviors. These data suggest that KOR inhibition of spinal neurons is a possible mechanism of KOR agonist-mediated analgesia.

Poster 21. – Mitchell Max Finalist - Session 3: May 25 – 11:40am

The influence of postural behavior and brain organization on progression of back pain symptoms in young adults: a prospective longitudinal study.

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Objective
The objective of this ongoing research is to understand how postural control of the trunk musculature and brain sensorimotor organization influence the persistence of low back pain (LBP) symptoms in young adults.

Specific aims
Aim 1 tests the hypothesis that postural control of the paraspinal and abdominal musculature differs in young adults with and without a history of LBP. Aim 2 tests the hypotheses that morphology, connectivity, and activation of brain sensorimotor networks differ in young adults with and without a history of LBP and that these characteristics associate with altered postural control. Aims 1 and 2 of the study also test the hypothesis that postural muscle activation and brain sensorimotor activation are modified in response to paraspinal muscle fatigue. Aim 3 tests the hypothesis that baseline postural control/sensorimotor organization predict symptom recurrence and progression over time, independent of prior symptom history and psychological predictors of poor outcome in LBP.

Background/methods
The highest incidence of new episodes of LBP occurs during young adulthood. We propose that reorganization of cortical and subcortical sensorimotor brain areas in response to LBP early in adulthood is associated with persistently altered postural control of the trunk musculature. Changes in postural control, including increased trunk muscle activation and co-activation, may result in adverse spinal loading that promotes recurrence or chronicity of symptoms over the lifespan. Increased paraspinal fatigability is another consequence of LBP. We hypothesize that altered postural control and brain sensorimotor activation may be exaggerated in young adults with a history of LBP in response to paraspinal muscle fatigue.

To accomplish our specific aims, we recruit young adults with a greater than one-year history of LBP and back-healthy controls. Paraspinal fatigue is induced using the isometric Sorensen endurance test. Postural control is quantified using electromyography pre- and post-fatigue during two anticipatory postural perturbation paradigms and during walking. For Aim 2 we assess gray matter density in brain sensorimotor regions and resting-state functional connectivity of sensorimotor networks. The sensorimotor brain activation associated with postural control in the trunk is quantified pre- and post-fatigue using a novel trunk perturbation paradigm. From baseline, back pain symptom intensity and impact are tracked over 18 months. Upon completion of the study, latent class analysis will be used to identify sub-classes within the LBP group based on symptom trajectory and to determine if Aim 1 and 2 neuromechanical factors predict sub-class membership.

Preliminary Results and Significance
Fifty-one individuals have been recruited to date, of whom 32 have LBP. Average (standard deviation) age is 22.3 (3.4) years. Individuals with LBP report average symptom intensity of 5/10 during episodes. Nine individuals report chronic LBP (pain on at least half of the days in the reporting period) while the rest meet the criteria for recurrent LBP, with less frequent symptomatic episodes. Aim 1: The LBP group have significantly greater paraspinal fatigability than back-healthy controls. Preliminary data suggest that young adults with LBP compensate for paraspinal fatigue with earlier anticipatory postural activation in the paraspinal musculature. Pre- and post-fatigue, the LBP group have greater co-activation in the paraspinal and abdominal muscles during walking. Aim 2: Preliminary data suggest a reduction in gray matter density in SMA in young adults with LBP. During the fMRI postural perturbation task, individuals with LBP have significantly greater activation in the primary motor cortices, supplementary motor areas, and inferior parietal cortices. Aim 3: There are highly heterogeneous symptom trajectories over time. To date, all participants have reported at least one LBP episode during the follow-up period.

When completed, this study will significantly increase the understanding of neuromechanical mechanisms that underlie recurrence, chronicity, and progression of LBP symptoms in young adults with LBP.

Poster 22. - Session 3: May 25 – 11:40am

Anterior cingulate inputs to nucleus accumbens control the social transfer of pain and analgesia

Monique L. Smith, Naoyuki Asada and Robert C. Malenka

OBJECTIVE: Empathy, the adoption of another's sensory and emotional state, plays a critical role in adaptive social interactions. Little is known about the underlying neural circuitry of empathy, and in particular, how distinct affective experiences are set apart within the brain. Thus, we set out to develop a multifaceted rodent model for empathy, and explore the underlying neural circuit mechanisms for this behavior.

SPECIFIC AIMS: The first aim was to optimize a protocol for the rapid social transfer of pain in order to create a paradigm conducive to neural circuit manipulations. Next, we utilized this protocol for the rapid social transfer of pain to interrogate the underlying neural circuitry. We then developed an experimental protocol for the social transfer of pain relief (analgesia) and compared the anterior cingulate (ACC)-dependent neural circuitry responsible for the social transfer of pain and analgesia to the ACC neural circuitry required for the social transfer of fear.

BACKGROUND: Pain can act as a social signal that can benefit not only the object of the pain, but the social group as a whole, as recognition of another's pain can lead to the avoidance of harm and trigger empathy and caregiving behavior. Empathy is the adoption of another's sensory or affective state, and this core social ability undoubtedly impacts pain experience, pain persistence, and treatment outcomes. Although, historically, empathy was often considered a high level affective-cognitive process experienced solely by humans, it is increasingly appreciated that many species including rodents display evolutionarily conserved behavioral antecedents of empathy. It is therefore possible to begin to define the neural mechanisms that mediate behavioral manifestations of empathy in species that are optimal for application of modern circuit neuroscience tools.

RESULTS AND SIGNIFICANCE: We found that a 1 hour social interaction between a "bystander" mouse and a cagemate experiencing inflammatory pain led to mechanical hyperalgesia in the bystander, which lasted 4 but not 24 hours. This social transfer of pain also led to thermal sensitivity, thermal place aversion, and affective changes that were detected by a conspecific. The social interaction led to activation of neurons in the ACC and several of its downstream targets including the nucleus accumbens (NAc), which monosynaptic rabies virus tracing (in a time and activity dependent manner) revealed was directly and functionally connected to the ACC. Bidirectional manipulation of activity in ACC to NAc inputs prevented the acquisition of socially transferred pain but not the expression of the mechanical sensitivity that was used to assay pain thresholds. A novel behavioral protocol revealed the rapid social transfer of analgesia, which also required activity in ACC to NAc inputs. In contrast, ACC to NAc input activity was not required for the social transfer of fear, which instead required activity in the ACC projections to the basolateral amygdala (BLA).

These experiments establish that mice can rapidly and reliably adopt the sensory-affective state of a social partner, regardless of the valance of the information (i.e. pain, fear, or pain relief). We demonstrate that the ACC generates specific and appropriate empathic behavioral responses through accessing distinct downstream targets. Specifically, ACC to NAc input activity is necessary for the social transfer of pain and analgesia but not the social transfer of fear, which instead requires ACC to BLA input activity. Elucidating circuit-specific mechanisms that mediate various forms of empathy in experimentally accessible animal models is necessary for generating hypotheses that can be evaluated in human subjects using non-invasive assays. More sophisticated understanding of evolutionarily conserved brain mechanisms of empathy will inform our understanding of the underlying mechanisms of caregiver burden, pain chronicity, and treatment outcomes in pain patients.

Poster 23. - Session 3: May 25 – 11:40am

Assessment of Spinal Cord Stimulation Induced Pain Relief in Chronic Pain Patients Using EEG

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Objective:
Develop quantified, neural signatures of pain relief in chronic pain patients.

Specific Aims:
Characterize the spatio-spectral features of tonic and novel SCS waveforms in intraoperative and clinical conditions in chronic pain patients and correlate these neural features to amount of pain relief as measured through recognized outcome measures.

Background:
Chronic pain is a significant problem. It has been estimated to affect more than 50 million adult Americans and remains one of the most common reasons that patients seek healthcare. Spinal cord stimulation (SCS) is an FDA-approved neuromodulation treatment to relieve chronic refractory pain. While SCS can be used effectively in many patients with refractory chronic pain conditions, a significant portion of the patients receive suboptimal or inadequate pain suppression. Alternative to the traditional stimulation (tonic), one strategy to improve clinical efficacy is using novel stimulation patterns such as burst and high frequency stimulation (HFS). Studies show that these patterns alter pain differently. HFS provides greater pain relief than tonic SCS, whereas burst stimulation has similar effects to tonic SCS on pain sensation but greater effects on affective pain components. Though, it is still unknown why some patients respond well to one stimulation pattern over another. In non-SCS patients, the frequency content and overall power of EEG signals has been found to be higher in chronic pain patients compared to controls. Furthermore, in chronic pain patients compared to healthy controls, the dominant peak frequency was found to be shifted towards lower frequencies and this shift in peak alpha frequency was correlated with longer pain duration. One study in SCS patients associated burst stimulation with increased alpha activity in dorsal anterior cingulate cortex and dorsolateral prefrontal cortex compared to baseline and tonic stimulation.

Results:
Our preliminary data suggests that changes in alpha peak frequency and ratio of alpha and theta band power might be correlated to SCS-induced pain relief. The intra-operative EEG demonstrates similar spatio-spectral patterns to post-operative EEG. Specifically, our findings show that pain relief is correlated best with increased alpha band power in frontal and somatosensory cortical regions in HFS.

Significance:
Through this study, we will gain insights into how SCS waveforms affect and how changes in neural oscillations shape the pain relief. Given that assessment of the pain relief by SCS depends almost exclusively on patient self-reports and lack of objective measurements of SCS implants results might lead to increased number of failed permanent placements, developing quantified, neural signatures of pain relief could form an objective metric for device selection, better pain management in patients with minimal pain relief, and lead to more personalized SCS therapy with higher efficacy. Furthermore, these achievements may advance development of new neurotechnologies that can guide therapeutic decision making and reduce the devastating impact of chronic pain.

Poster 24. - Session 3: May 25 – 11:40am

Uncontrolled Pain and Risk for Mental Health Disorders Among Patients with Alzheimer's Disease and Related Dementia

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Objective: Our objective is to understand the role of pain control as a preventive solution in reducing mental health disorders that are highly prevalent and debilitating among patients with Alzheimer's Disease and Related Dementia (ADRD). The long-term goal is to establish epidemiologic evidence for advancing insight into strategies that may break the cycle between uncontrolled pain and mental health disorders in ADRD.

Specific Aim: To examine the extent to which uncontrolled (vs. controlled) pain is associated with an increased risk for select mental health disorders, including depression, behavioral symptoms, anxiety, and sleep disorders in patients with ADRD who had chronic noncancer pain.

Background: Mental health disorders, such as depression, behavioral symptoms, anxiety, and sleep disorders, affect 97% of people with ADRD at some point in time during the disease course and are one of the main reasons for nursing home admission. Although pain has been implicated as an important risk factor for these disorders, the magnitude of risk conferred by uncontrolled pain remains unclear. Available effect estimates have been inferred from cross-sectional studies that show a higher prevalence of mental health disorders, such as depression and behavioral symptoms, among ADRD patients with versus without pain. To date, limited cohort studies have assessed the association between uncontrolled pain and risk for mental health disorders, and findings regarding pain control and risk for some mental health conditions are inconsistent. These inconsistencies may be due to small sample sizes, outdated data, and most importantly, failure to account for the time-varying feature of pain and confounders (e.g., use of pain medications), which can result in biased estimations of pain control on mental health outcomes. To address these study limitations, we conducted a retrospective cohort study of a 5% Medicare sample linked to the Minimum Data Set (MDS), version 3.0, from 2011 to 2015 to examine the associations between controlled pain and mental health disorders among patients with ADRD who were long-term residents of nursing homes.

Results and Significance: We hypothesized that patients with uncontrolled pain, compared to those with controlled pain have a higher risk for onset of mental health disorders. We identified 4 distinct cohorts of patients with ADRD who had no depression (defined as ≥10 on the Patient Health Questionnaire 9), no behavioral symptoms (presence of psychotic or aggressive behaviors documented in MDS 3.0), no diagnosis of anxiety, and no diagnosis of sleep disorders, respectively, 6 months before or at cohort entry (i.e., date of the first eligible quarterly MDS pain assessment). Uncontrolled pain—the key exposure— was defined as a numerical rating scale >4, verbal descriptor scale of moderate or severe pain, or ≥1 pain indicators on the Checklist of Nonverbal Pain Indicators. The final sample size ranged from 15,658 to 38,763 patients, with a mean follow-up of 1.6 years. After applying the marginal structural modeling approach that accounts for time-varying pain control exposure and time-varying confounders, we observed that uncontrolled pain was associated with 67% increased risk for depression (95% CI, 1.54-1.81), 28% increased risk for behavioral symptoms (95% CI, 1.19-1.37), 44% increased risk for anxiety (95% CI, 1.35-1.54), and 68% increased risk for sleep disorders (95% CI, 1.54-1.82). The findings were consistent across sensitivity and subgroup analyses. Our findings are significant in that they demonstrated uncontrolled pain is associated with increased risk for the select mental health disorders in a population-based sample of patients with ADRD. Pain control may serve as a modifiable factor for reducing the risk of mental health disorders in patients with ADRD.

Poster 25. - Session 3: May 25 – 11:40am

Neural invasion by oral cancer and pain – the Schwann cell story

Yi Ye, Elizabeth Salvo, Tu Nguyen, Kesava Asam, Bradley Aouizerat

Objective: To gain greater mechanistic insight on how oral cancer cells invade into the nerve (*i.e.*, perineural invasion, PNI) and promote pain.

Specific aim(s):

1. Determine pain phenotype, differentially expressed genes and perturbed molecular pathways in oral cancer PNI.
2. Determine if Schwann cells increase oral cancer invasiveness and contribute to oral cancer pain.

Background: Cancer invading into nerves, termed perineural invasion (PNI), is a painful condition and associated with poor patient survival. The cellular and molecular mechanisms underlying oral cancer PNI and associated pain are poorly understood. Emerging evidence suggests Schwann cells, the peripheral glia, play an important role in cancer growth, migration, and dispersion, facilitating cancer invading into the nerve. Schwann cells are essential for nerve function, regeneration, and repair. In response to injury, Schwann cells breakdown myelin, convert into a dedifferentiated phenotype and release pain mediators, contributing to neuropathic pain. It is yet unknown, whether Schwann cells are involved in oral cancer PNI and associated pain. We hypothesize that cancer cells trigger an injury response in Schwann cells, which in turn promotes oral cancer invasiveness, facilitating PNI and associated pain.

Results and Significance: To gain a better understanding of pain experienced by oral cancer patients with PNI, we compared pain in oral cancer patients with and without PNI evaluated with a validated oral cancer pain questionnaire. We

performed gene expression and pathway analysis of oral cancer patients with and without PNI using the publically available The Cancer Genome Atlas data (TCGA). We produced a mouse model of PNI, characterized pain-like behaviors, and examined nerve damage using electron microscopy. We measured oral cancer cell proliferation, migration, and invasion in the presence of Schwann cells. Our results show that oral cancer patients with PNI report greater spontaneous pain and mechanical allodynia compared with patients without PNI, suggesting unique mechanisms drive PNI-induced pain. In the TCGA data containing 99 tongue cancer patients with PNI, we identified 18 differentially expressed genes and six perturbed molecular pathways that have known implications in either cancer progression or neuronal function including pain. In the mouse sciatic nerve PNI model, mice with PNI exhibited spontaneous nociception and mechanical allodynia. PNI resulted in nerve injury, such as axon degeneration and loss, as well as Schwann cell abnormalities in the mouse model. We found that in the presence of Schwann cells, oral cancer cells become more proliferative, migratory, and invasive. Cancer induces Schwann cells to become more proliferative and migratory. Cancer-conditioned Schwann cells induced increased pain-like behaviors in mice. Our future studies will focus on identifying the molecular signal within the tumor microenvironment that triggers the injury response in Schwann cells, and whether we can target Schwann cells to reverse PNI and associated pain.

Our results improved our understanding of pain phenotypes experienced by patients with PNI. We generated an animal model to study cellular and molecular mechanisms of PNI and provided direct evidence of nerve injury associated with PNI. Our study will contribute to a better understanding of the role of Schwann cells in facilitating cancer progression and associated pain.

Poster 26. - Session 3: May 25 – 11:40am

MEASURES OF CARDIOVASCULAR FUNCTION SUGGEST AUTONOMIC NERVOUS SYSTEM DYSREGULATION AFTER SURGICAL INDUCTION OF JOINT INJURY IN THE MALE LEWIS RAT.

Taylor D. Yeater, Jasenka Zubcevic, and Kyle D. Allen

Purpose: Functional changes in the autonomic nervous system may help explain variability in the progression of knee osteoarthritis (OA) pathology and symptoms. The autonomic nervous system (ANS) is comprised of two branches, the parasympathetic and sympathetic nervous systems with reciprocal effects on involuntary actions throughout the body, such as heart rate. Thus, heart rate parameters may be used as an indicator of autonomic dysregulation.

Autonomic balance is dysregulated in chronic inflammatory diseases, such as rheumatoid arthritis and hypertension, among others. To be clear, the etiologies of these diseases are different, but the commonality is inflammation that fails to resolve. Similarly, OA presents with chronic inflammation, but OA-related inflammation is low-grade and local, often failing to alter circulating levels of cytokines. Despite the emerging evidence for ANS dysregulation in inflammatory joint conditions, changes have not yet been characterized in a rodent model of OA.

Methods: Blood pressure measurements were collected longitudinally via radio-telemetry probes. Then, heart rate was derived from peaks in pulse pressure. Heart rate was evaluated as an indirect assessment of vagal nerve function, a key part of the ANS. Measurements were collected for 5 minutes each hour for 24 hours and analyzed separately for high activity and low activity periods. Recordings occurred at baseline and every other week for 8 weeks after induction of OA via medial collateral ligament transection plus medial meniscus transection (MCLT+MMT) or MCLT alone, with skin incision used as a control. Because stress is known to exaggerate autonomic responses, characteristics of heart rate responses to novel environment stress were also assessed. A 5-HT3a agonist, 1-phenylbiguanide, with reported vagal activation properties was used to indirectly assess vagal nerve function. Heart rate and blood pressure responses to the 5-HT3a agonist were recorded in anesthetized rats. Cardiac vagal responses were also indirectly assessed in response to mechanical stimuli at the knee.

Results: Heart rate varied between groups during the low activity period ($p<0.05$, main effect) with MCLT and MCLT+MMT having lower heart rate than the control group ($p=0.017$ and 0.018, respectively). Additionally, MMT animals showed decreased high frequency power (parasympathetic tone) compared to control and MCLT groups ($p<0.01$) during the high activity period. The ratio of low frequency to high frequency power (sympathovagal balance) was higher in MCLT+MMT animals compared to skin incision during high activity ($p<0.01$). During novel environment

stress, the ratio of low frequency to high frequency power tended to decrease in control and MCLT animals ($p=0.06$, group main effect). In anesthetized animals, mechanical stimuli at the knee caused a drop in heart rate and blood pressure; with no differences between groups. Finally, MCLT and MCLT+MMT animals displayed a larger drop in heart rate due to a 5-HT3a agonist, though not statistically significant.

Conclusions: Measurement of cardiovascular responses to pharmacological stimulation of 5-HT3a receptors, which are reportedly able to induce acute cardiac vagal responses, demonstrate for the first time a shift in ANS function in rodent knee injury models of OA. Our data suggest a sensitization of cardiac vagal activation to 5-HT3a agonist in OA groups, which was also supported by the tendency for a more prominent chronic reduction in heart rate in OA groups. Lastly, acute mechanical stimulation of the knee produced an immediate reduction in heart rate, suggesting a direct neural joint-brain connection that may modulate autonomic responses in OA. Although we did not observe group differences in these responses, further studies should delineate this using direct measurements of vagal nerve activity in response to mechanical stimulus of the joint in OA.