

The UF Pain Research &  
Intervention Center of Excellence  
(PRICE)

Pain Research Day 2015  
May 29, 2015

Keynote Presentation by Dr. Sean Mackey  
Stanford University, School of Medicine



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# TABLE OF CONTENTS

Pain Research Day Schedule of Events ..... 6

## POSTER ABSTRACTS

#1 Comparison between methods of generating temporal summation of second pain..... 7

#2 Age differences in habituation to prolonged noxious heat stimulation .. 8

#3 Experimental pain sensitivity and clinical pain severity in Asian Americans compared to non-Hispanic whites with knee osteoarthritis ..... 9

#4 Treatment preference, equipoise, and expectations: what you expect is what you get..... 10

#5 Does the application of transvaginal lidocaine modify pain sensitivity in women with chronic pelvic pain?..... 11

#6 Weekly pain variability as a predictor of fatigue in symptomatic knee osteoarthritis ..... 12

#7 Utilization of treatment approaches for spine and osteoarthrosis pain among medicare beneficiaries..... 13

#8 Physicians weigh virtual human patient characteristics more heavily than dentists when making pain-related clinical judgments ..... 15

#9 Integrating nervous system pain processing and resultant motor behavior: a conceptual model ..... 17

#10 Neural correlates of high intensity and low intensity pain ..... 18

#11 Beta power correlates of pain-induced changes in voluntary movement ..... 19

#12 Age-related differences in immune response to experimental pain in healthy individuals ..... 20

#13 Effect of an aerobic exercise intervention on pain scores. A study design..... 21

#14	Influence of testing modality on first, second, and temporal summation pain.....	22
#15	Evidence for a central disorder of pain in PD and its relevance to PD cognition.....	23
#16	Longitudinal assessment of connectivity across resting-state networks in a model of acute low back pain.....	24
#17	Exploring experience dependent changes in pain sensitivity using an exercise-induced injury as a model of acute low back pain.....	26
#18	Salivary cortisol and fMRI-based measures of central sensitization following sham intervention for acute musculoskeletal pain.....	28
#19	Toward clinical decision support for chronic pain: integrating patient reported outcomes in an electronic health record.....	30
#20	Pain modulation profiles for patients with fibromyalgia and myofascial pain syndrome using REsponse-Dependent STIMulation.....	32
#21	Pain and related symptoms reported by patients with chronic graft-versus-host disease and relationships among markers of inflammation and quality of life.....	33
#22	Changes in synovium and subchondral bone correlate with heightened limb sensitivity in a rat model of post-traumatic osteoarthritis.....	35
#23	Influences of pain self-efficacy on pain catastrophizing: evidence for mediation and moderation roles in outpatient orthopedic physical therapy	37
#24	Dysfunction of endogenous pain inhibition following acute aerobic exercise in healthy older adults.....	38
#25	Associations between omega-6: omega-3 ratio, knee osteoarthritis pain and omega-3 supplementation.....	39
#26	Monocytic cell responsiveness and estrogen-related influences on inflammation in TMD pain.....	40
#27	Comorbidities associated with patients attending an academic family medicine pain management program.....	41
#28	Establishing a pain management program within a university based family medicine residency.....	42

**#29 Evaluation of the first 100 patients at chronic pain management program at main (CPM2)..... 43**

**#30 Placebo analgesia enhances descending pain-related effective connectivity: a dynamic causal modeling study of endogenous pain modulation ..... 44**

**#31 Optimizing chronic pain treatment with enhanced neuroplastic responsiveness ..... 45**

**#32 Central pain processing measures are associated with movement-evoked pain report among older adults with chronic axial low back pain .... 46**

**#33 Effect of spinal manipulations and body-based interventions in a model of experimentally induced low back pain ..... 48**

**#34 Role of participant expectations in clinical outcomes in subjects with neck pain..... 49**

**#35 Finding good TEMPOS with the SAX: preliminary definitions of temporal postoperative pain signatures via symbolic aggregate approximation ..... 50**

**#36 Is acute pain medicine ready for Markov? Preliminary testing of sequential postoperative pain intensity transition matrix stabilities ..... 52**

**#37 When does postoperative pain resolve? Differences in time to onset of durable effective acute postoperative pain relief (DEAPPR) ..... 53**

**#38 Experimental pain phenotyping in older adults with knee osteoarthritis ..... 54**

# Pain Research Day Schedule of Events

Friday May 29, 2015

Time	Activity	Location
8:30 AM	Dr. Fillingim picks up Dr. Mackey at hotel	Hilton
9:00-10:00 AM	PRICE Lab Meeting	CTRB 3256
10:15-11:00 AM	Chris Harle & iPro Team along with PMP Team (Lari Cavalleri & Amanda Elsey)	CTRB 3256
11:00-11:45 AM	Meeting with PRICE Junior faculty	CTRB 3256
12:00-1:30 PM	Lunch with trainees (Postdocs and graduate students)	CTRB 3161
1:45-2:45 PM	Meeting with Steve George, Mike Robinson, Mark Bishop, Roland Staud	MBI LG-110
3:00-4:00 PM	Keynote presentation Brain Imaging Biomarkers for Pain: Scientific Ethical and Legal Implications	MBI, Deweese Auditorium
4:15-6:00 PM	Reception and Poster Session (Faculty, Trainees, Guests and Dr. Mackey)	CTRB Lobby
6:30 PM	Dinner (PRICE faculty and Dr. Mackey)	TBA

**#1 TITLE: Comparison between methods of generating temporal summation of second pain.**

**AUTHORS: Maria Aguirre, Yenisel Cruz-Almeida, Roger B. Fillingim, Joseph L. Riley III**

Temporal summation of second pain (TS) results in an increase in pain from repetitive stimulation of peripheral C-fibers. Typically, short discrete heat pulses are administered to skin spaced by up to 3-sec and the delayed sensation is rated. There are two general designs of thermal testing apparatus for testing TS; systems that intermittently contact the skin using preheated thermodes and continuous-contact thermodes that rapidly cycle between wide ranges of temperatures. The intermittent method has been criticized because the recurrent contact contributes to inhibition of pain. This study compared two sets of data, each using one of these methods. The first sample consisted of 102 subjects (46 males and 56 females, ages 18-77) using an intermittent-contact protocol (IC-TS). Another consisted of 75 subjects (35 males and 40 females, ages 18-77) using a constant-contact protocol (CC-TS). The IC-TS protocols used a stimulus contact interval of 0.8-sec and an inter-stimulus-interval (ISI) of 2.5-sec and 3.5-sec. The CC-TS protocol consisted of rise time of 0.4-sec, peak time of 0.5-sec; return time of 0.4-sec with inter-pulse intervals of 2.0 and 3.0 for a 3.3-sec and 4.3-sec pulse sequence which is the equivalent timing as the IC-TS. Subjects rated pain between each of 10 heat stimulus administrations using a 0-100 scale. Using the IC-TS methodology, mean increases in pain across the 10 trials was significantly different ( $p=.021$ ) between the 2.5-sec (mean=33.8, SD=19.6) and 3.5-sec (mean=23.3, SD=19.7) protocols. The CC-TS methodology resulted in mean increases in pain that was not significantly different ( $p=.534$ ) between the 3.3-sec (mean=12.8, SD=10.7) and 4.3-sec (mean=10.3, SD=10.8) pulse sequences. This data indicates that the intermittent-contact method resulted in greater TS than the constant-contact method and demonstrated sensitivity to the two ISIs and support the use of protocols using the intermittent-contact method to generate TS.

## #2 TITLE: Age differences in habituation to prolonged noxious heat stimulation

**AUTHORS:** Maria A. Aguirre, Kelly M. Naugle, Yenisel Cruz-Almeida, Joseph L. Riley III.

Habituation is the decrease of pain with repetitive painful stimulation involving both peripheral and central mechanisms and may play an important role in protection against the development of chronic pain. While previous research indicates that aging is associated with deficient pain modulatory mechanisms, age differences in habituation have been poorly characterized. Thus, the purpose of this study was to investigate differences in habituation of prolonged heat pain in older adults compared to younger adults. Twenty-one healthy young adults (mean age  $21.3 \pm 6.7$ ) and nine healthy older adults (mean age  $67.2 \pm 3.0$ ) completed five 30s prolonged heat trials at the glabrous skin of the palm over a forty-five minute timeline [Trial 1 (T1)-baseline, T2-10 min after baseline, T3-15 min after baseline, T4-30 min after baseline, T5-45 min after baseline]. Subjects rated pain continuously during each 30-s trial on a 0-100 scale. Area under the curve (AUC) of the heat pain ratings was calculated for each trial and analyzed with a 2Age  $\times$  5Time mixed model ANOVA with sex and thermode temperature as covariates. The results indicated a significant interaction between time and age group across heat trials. Follow-up tests indicated that AUC decreased significantly from T1 ( $934.39 \pm 109.82$ ) to T5 ( $644.81 \pm 107.89$ ) in younger adults. In older adult, the AUC significantly increased from T1 ( $838.09 \pm 174.06$ ) to T5 ( $1144.77 \pm 171.00$ ). Finally, while no significant age group differences were found for T1, older adults exhibited significantly greater AUC for trials 4 and 5 compared to younger adults. Our findings indicate that while younger adults habituate to repeated trials of prolonged heat pain over a 45-minute time span, older adults sensitize and experience greater pain across trials. These age differences in pain modulation mechanisms may have important implications for the increased development and maintenance of chronic pain in older adults. This study was funded by NIH-NIA grant R01AG039659.

**#3 TITLE: Experimental pain sensitivity and clinical pain severity in Asian Americans compared to non-Hispanic whites with knee osteoarthritis**

**AUTHORS: Hyochol Ahn, Roger Fillingim, Debra Lyon, Cynthia Garvan, Eunyoung Choi**

There are 17.3 million Asians in the United States, and Asian American was the fastest growing ethnic group in the United States, increasing by 46% between 2000 and 2010. Ethnic and racial group differences in pain are often reported in the literature, but most studies have been limited to other minority groups (e.g. African American and Hispanic American), and few studies have examined ethnic group differences in pain among Asian Americans. Thus, the aim of this study was to compare ethnic group differences in experimental pain sensitivity and clinical pain severity between Asian Americans and age- and gender-matched non-Hispanic whites with knee osteoarthritis pain. Data were collected from 50 Asian Americans ages 45-85 with symptomatic knee osteoarthritis pain. Data for age and gender matched comparison of 50 non-Hispanic whites were obtained from a prior study "Understanding Pain and Limitations in Osteoarthritic Disease (2012-2014)." The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Graded Chronic Pain Scale (GCPS) were used to assess the severity of clinical knee pain. Quantitative sensory testing was used to measure experimental sensitivity to heat pain, pressure pain, and punctate mechanical pain. Participants had a mean age of 55 years (SD =  $\pm$  8 years), and the majority were female (62%). Asian Americans with knee osteoarthritis displayed significantly greater sensitivity to heat pain, pressure pain, and punctate mechanical pain compared to non-Hispanic whites ( $P < .001$  for all). Moreover, Asian Americans had significantly higher levels of clinical pain and disability. These findings add to the growing literature regarding ethnic and racial influences in pain. Further investigation is needed to identify the mechanisms underlying these ethnic group differences in pain between Asian Americans and whites, as well as to ensure that ethnic group disparities in pain are ameliorated.

#### **#4 TITLE: Treatment preference, equipoise, and expectations: what you expect is what you get**

**AUTHORS: Meryl Alappattu, Joel Bialosky, Charles Gay, Mark Bishop**

Expected pain-relief from treatment is associated with positive clinical outcomes in patients with musculoskeletal pain. Less widely studied is the preference of the provider and patient for one type of treatment approach over others. The purpose of this study was to evaluate the extent to which these variables, the type of treatment received, and expectations for pain relief influenced pain intensity in an experimental model of low back pain. Healthy individuals were randomly assigned to receive manipulation (MAN), mobilization (MOB), or therapeutic touch (TT) 48 hours after an eccentric exercise protocol designed to induce acute low back pain. General linear modeling (GLM) was used to evaluate the contributions of expected pain relief, subject and provider treatment preference, and treatment received to pain relief immediately following MAN, MOB, or TT. Pain intensity was measured using the 101-point Numerical Pain Rating Scale. Data from 65 subjects (75.4% female, mean age 22.8) and 3 providers comprised the sample. No group differences existed in pre- and post-intervention pain intensity scores. Two providers expected SMT to provide the greatest pain relief and one did not have a preference. Twenty-four subjects (36.9%) had no treatment preference, four (6.2%) preferred MAN, 17 (26.2%) preferred MOB, and 20 (30.8%) preferred TT. GLM results indicated that subject expectation for pain relief significantly predicted pain relief (Wald $\chi^2=72.8$ ,  $p<0.001$ ). A significant interaction existed between treatment received and whether preference matched treatment; specifically, when a provider and subject had no preference about treatment, MAN was associated with pain relief (Wald $\chi^2=4.2$ ,  $p=0.04$ ). These data extend previous work related to expectations for pain relief to an acute model of low back pain. Our results suggest that individuals' expectations for pain relief strongly predicted pain outcomes. Future work should extend these findings beyond the immediate time point.

**#5 TITLE: Does the application of transvaginal lidocaine modify pain sensitivity in women with chronic pelvic pain?**

**AUTHORS: Meryl Alappattu, Steven George, Michael Robinson, Roger Fillingim, Nash Moawad, Emily Weber LeBrun, Mark Bishop**

The purpose of this study is to examine the extent to which 2% lidocaine gel applied to the vaginal mucosa affected local and remote pain sensitivity in women with pelvic pain. Women with pelvic pain  $\geq 3$  months underwent a natural history (NH) session consisting of quantitative sensory testing (QST) using local and remote pressure stimuli and remote thermal stimuli. They were randomized to 2 additional sessions to receive 2% lidocaine (VL) or placebo (VP; sterile lubricant) over the vaginal mucosa. Repeated-measures multivariate analyses of variance (MANOVAs) were conducted for pain intensity, pressure pain threshold (PPT), and heat threshold (HT<sub>h</sub>) and tolerance (HT<sub>ol</sub>). Time and condition served as the within subjects factors.

The MANOVA for pain ratings indicated significant effects for condition ( $\theta=3.76$ ,  $F(9,9)=3.76$ ,  $p=0.03$ ) and time ( $\theta=1.04$ ,  $F(9,27)=3.11$ ,  $p=0.01$ ). Follow-up ANOVAs showed significant condition effects with lower PPT pain ratings at the upper vestibule ( $F(2,16)=10.28$ ,  $p=0.001$ ) and lower vestibule ( $F(2,16)=4.36$ ,  $p=0.03$ ) in VL compared to NH. HT<sub>ol</sub> ratings were significantly lower at baseline and 15-min compared to 60 minutes ( $F(1.83,14.63)=4.92$ ,  $p=0.003$ ). The MANOVA for PPT and temperature indicated significant effects for a time\*condition interaction ( $\theta=1.17$ ,  $F(9,63)=5.33$ ,  $p<0.0001$ ). Follow up ANOVAs showed two significant time\*condition interactions. PPT was significantly higher at 60 minutes compared to baseline with VL and VP compared to NH ( $F(8,64)=2.64$ ,  $p=0.02$ ). HT<sub>ol</sub> was significantly higher at 30 minutes compared to baseline with VL and VP compared to NH ( $F(8,64)=3.10$ ,  $p=0.005$ ). VL reduced pain ratings at the vestibule compared to NH but not compared to VP. VP and VL were associated with higher HT<sub>h</sub> and HT<sub>ol</sub> temperatures compared to NH. The lack of significant effects at some local and remote sites indicates that solely treating the local pelvic region with lidocaine may be insufficient to reduce widespread pain sensitivity.

## #6 Weekly pain variability as a predictor of fatigue in symptomatic knee osteoarthritis

**AUTHORS:** Emily J. Bartley, PhD; Christopher D. King, PhD; Yenisel Cruz-Almeida, PhD; Kimberly T. Sibille, PhD; Burel R. Goodin, PhD; Toni L. Glover, PhD GNP-BC; Laurence A. Bradley, PhD; & Roger B. Fillingim, PhD

Pain variability has emerged as a significant predictor of health-related functioning, with higher levels of variability associated with affective dysregulation and poorer adaptive coping. While pain in older adults has been widely examined, few studies have addressed the role of pain variability in physical and psychological health outcomes. Therefore, the aims of the current study were to examine whether variability in pain report predicted fatigue, sleep, and mood over a period of 3 months in older adults with knee osteoarthritis (OA), as well as identify demographic and affective correlates of high pain variability. A total of 289 participants with symptomatic knee OA (127 Caucasian-Americans, 162 African-Americans) completed a battery of psychosocial questionnaires, as well as weekly telephone-based surveys assessing average pain intensity and behavioral measures (i.e., fatigue, sleep, mood) across 3 months. Pain variability was measured by examining intra-individual standard deviations of weekly pain scores, and hierarchical multiple regression analyses were used to assess whether pain variability predicted fatigue, sleep, and mood. After controlling for the effects of relevant demographic variables, weekly variability in pain predicted greater fatigue at months 2 ( $\beta=.14$ ,  $p<.05$ ) and 3 ( $\beta=.12$ ,  $p<.05$ ). However, sleep and mood were not significantly associated with pain variability ( $p's>.05$ ). Additional analyses revealed that females and African-Americans, as well as individuals with lower income and education had greater variability in weekly pain report ( $r's=-.12$  to  $-.30$ ). Additionally, higher levels of catastrophizing, passive coping, and pain hypervigilance were associated with more pain variability ( $r's=.16$  to  $.51$ ). Overall, results suggest that greater fluctuations in pain may enhance fatigue symptomatology, and higher pain variability may be correlated with various psychosocial/demographic patient characteristics. Further research is warranted to examine whether clinical interventions for pain variability may be a potential target for ameliorating fatigue and explore individual factors associated with high pain variability.

**#7 TITLE: Utilization of treatment approaches for spine and osteoarthritis pain among medicare beneficiaries**

**AUTHORS: Jon C. Mills, MBA, Trevor Lentz, MPT, CSCS, Sarah E. Bauer, MPH, Heidi Kinsell, PhD(c), Ivana A. Vaughn, MPH, Steven Z. George, PT, PhD, Roger Fillingim, PhD, Jeffrey Harman, PhD**

Background: Spine and osteoarthritis pain represent two of the most commonly diagnosed pain conditions among Medicare beneficiaries, accounting for significant levels of disability and healthcare expenditures. Little is known about treatment utilization patterns among patients with pain in this population. The aim of this study was to identify treatment approaches for these pain conditions among Medicare beneficiaries. A better understanding of treatment utilization patterns is necessary prior to performing comparative and cost-effectiveness analyses.

Methods: We conducted an observational study using the Medicare Current Beneficiary Survey (MCBS) from 2006 to 2010. Patients were identified as having a spine or osteoarthritis pain condition using the primary ICD-9 code from physician claim files. Non-surgical treatments were identified from physician and pharmacy claims files. Frequencies of treatment approaches used are reported on the person level using weighted analysis.

Results: From 2006-2010, 7,278 beneficiaries were diagnosed with spine pain and 3,923 with osteoarthritis pain in the MCBS sample. Among beneficiaries diagnosed with spine pain, the most commonly used treatments included (% of patients): prescription medication (68%), chiropractic manipulation (24%), injection (16%), physical modalities (11%) and exercise (10%). Among beneficiaries diagnosed with osteoarthritis, the most commonly used treatments included: prescription medications (68%), injection (22%), exercise (4%), physical modalities (2%) and manual therapy (2%). Among patients receiving a pain medication for spine and osteoarthritis conditions, opioids were the most commonly prescribed pain medication (85% and 87%, respectively).

Conclusions: Our results show that there is considerable variation in the types of treatments used for osteoarthritis and spine pain. Future research should compare health outcomes and costs associated with different treatments for these pain conditions. Utilization of the most effective treatment options in terms of health outcomes and costs have the potential to reduce the economic burden and improve the quality of life for patients with these common pain conditions.

## **#8 TITLE: Physicians weigh virtual human patient characteristics more heavily than dentists when making pain-related clinical judgments**

**AUTHORS: Jeff Boissoneault, Ph.D., Emily J. Bartley, Ph.D., Jennifer M. Mundt, M.S., Laura D. Wandner, Ph.D., Adam T. Hirsh, Ph.D., Michael E. Robinson, Ph.D.**

Objective. Disparities in health care associated with patient sex, race, and age are well documented. Previous studies using virtual human (VH) technology have demonstrated that provider characteristics may play an important role in pain management decisions. However, these studies have largely used only nomothetic analyses emphasizing group differences. In the current study, we employed an idiographic design (i.e., LENS model) to determine the weight associated with VH characteristics applied by each participant in making clinical judgments, then conducted follow-up nomothetic analyses to identify provider characteristics associated with the VH cue weights.

Methods. Providers (N=152; 76 physicians, 76 dentists) viewed video vignettes of VH patients varying in sex, race, and age. They provided computerized ratings of VH patients' pain intensity and unpleasantness, and also reported their willingness to prescribe non-opioid and opioid analgesics for each patient. Regression analyses were conducted for each participant;  $\beta$ -weights associated with each VH cue were then subjected to sex X race X profession ANOVA.

Results. Analyses indicated physicians had significant greater  $\beta$ -weights associated with VH age cues for all ratings ( $p < 0.001$ ; Cohen's  $d > 0.69$ ). For ratings of pain intensity and willingness to prescribe non-opioid analgesics, effects of profession were qualified by provider race and both provider race and sex, respectively. For pain intensity, professional differences were present among minority but not White providers. For prescription of non-opioid analgesics, professional differences were present among all groups except minority men.

Conclusions. Results of this study highlight the

interaction of patient and provider factors in driving clinical decision-making. Although profession was related to use of VH age cues in making pain-related clinical judgments, this relationship was modified by providers' personal characteristics. Additional research is needed to understand what aspects of professional training or practice may account for differences between physicians and dentists.

**#9 TITLE: Integrating nervous system pain processing and resultant motor behavior: a conceptual model**

**AUTHORS: Katie A. Butera, Emily J. Fox, and Steven Z. George**

Background: The existing body of evidence suggests that motor behavior is altered by pain, but subsequent functional consequences are not well understood. Pain research has focused on affective, cognitive, and sensory components of the pain experience resulting in widely accepted peripheral and central pain processing pathways. However, dynamic sensorimotor interactions in the presence of pain have not been as clearly elucidated. Therefore, reasons for why altered motor behavior persists beyond a protective pain state and delay recover are unclear.

Proposed Model: We proposed a novel, conceptual model that integrates affective, cognitive, and sensorimotor components of nervous system pain processing. This model suggests dynamic interactions between these components collectively impact resultant motor behavior. In this model motor behavior is operationally defined as 1) the spectrum of altered movement that occurs when in a painful state (e.g. limping, reduced gait speed) and 2) providing sensorimotor feedback that further influences nervous system processing. Thus, pain affects movement through many dynamic, interactive pathways, but movement in turn affects pain through sensorimotor feedback loops. The model further outlines how motor behavior may strongly influence the course of recovery.

Conclusions: This conceptual model describes how affective, cognitive, and sensorimotor components interact to impact motor behavior. Specifically, the model emphasizes that resultant motor behavior may lead to variable recovery paths including rapid resolution of pain, prolonged recovery time, or a persistent, chronic pain state. The theoretical framework presented provides a platform for testing hypotheses to advance understanding of motor implications and functional consequences of pain conditions.

**#10 TITLE: Neural correlates of high intensity and low intensity pain**

**AUTHORS: Gaurav Misra, Edward Ofori, Jae Chung, Stephen A. Coombes.**

Pain is associated with reductions in power in alpha and beta bands, and increases in power in theta and gamma bands. Current knowledge is based on studies that have used short duration laser or electrical stimuli, delivered pain intensity at a single amplitude, and focused on single electrodes over the sensorimotor cortex. However, emerging evidence shows that gamma band power is increased in medial prefrontal regions during tonic (10 minutes; thermal) but not a phasic (1-15ms; laser) pain-eliciting stimulus. In the current study we use a 4 second thermal stimulus to elicit ongoing low pain and high pain while recording high density electroencephalography. We implemented a novel whole brain analysis based on independent component analysis, source localization and measure projection. Our analyses revealed increased gamma power in the medial prefrontal cortex which scaled progressively with pain perception. Consistent with previous evidence, reductions in power in alpha and beta bands were also found bilaterally in sensorimotor cortex and medial prefrontal cortex, but pain ratings did not correlate with changes in power at these frequencies. Our findings therefore extend the current literature by demonstrating that the association between gamma power in medial prefrontal cortex and pain perception can be captured by the presentation of a relatively short duration pain eliciting thermal stimulus, and point to the importance of brief versus ongoing pain eliciting stimuli when assessing the neural basis of pain.

## **#11 TITLE: Beta power correlates of pain-induced changes in voluntary movement**

**AUTHORS: Gaurav Misra, Edward Ofori, Jae Chung, Stephen A. Coombes.**

How pain affects movement is a subject of extensive research. Several electroencephalography (EEG) studies on the effect of pain on movement have made the onset of pain and onset of movement either concurrent or dependent. A movement made in response to a painful stimulus is akin to reacting to pain, and this has been associated with slower reaction times. However, a movement made in the presence of ongoing pain but in response to an innocuous cue is akin to working through pain, which is very different from reacting to pain. Often people work through pain rather than react to it. Working through pain often results in adaptation of motor strategies and changes in motor performance. The goal in the current study was to determine whether the initiation and execution of movement is also negatively influenced by ongoing pain. EEG studies of pain have demonstrated a pain-induced reduction in power in the alpha and beta bands. EEG motor studies have also demonstrated a movement-induced reduction in power in the same frequency bands, which suggests that pain may prime the motor system for movement and lead to a facilitation of movement initiation. To test this hypothesis, healthy subjects performed a visually guided ballistic elbow flexion task in the middle of a 4 second long thermal pain stimulus while we recorded EMG signals from the arm and high density EEG signals from the scalp. We implemented a novel whole brain analysis based on independent component analysis, source localization and projection of EEG measures on a 3D grid for averaging across subjects. We found that ongoing pain shortens reaction time significantly but does not affect movement velocity, acceleration and accuracy. The shortening was due to a reduction in pre-motor time and not due to a reduction in motor time (electro-mechanical delay). Spectral power in the beta band was source-localized to the contralateral sensorimotor cortex and was reduced significantly in the presence of pain. Further, beta power correlated positively with reaction time and pre-motor time but not with motor time. Hence, the mechanism of pain-induced shortening of reaction time cannot be peripheral but must be central in origin. Our findings demonstrate that ongoing pain can facilitate the initiation of movement.

**#12 TITLE: Age-related differences in immune response to experimental pain in healthy individuals**

**AUTHORS: Cruz-Almeida Y, Aguirre MA, Tighe P, Wallet S, Riley JL III**

Older adults experience greater clinical pain and are at a greater risk of developing chronic pain compared to younger adults. Potential contributors to this increased risk for chronic pain include the age-related deterioration of the immune and neuroendocrine systems. However, no studies have characterized immune and neuroendocrine biomarkers in response to experimental pain in healthy older adults without chronic pain. The aim of our study was to quantify the pain-evoked changes in several biomarkers in the context of experimental pain stimulation. Healthy younger and older adults (n=17) participated in 3 randomized laboratory sessions where experimental heat and cold pain and a control warm stimuli were administered over four minutes on separate days. Blood samples were collected before and after stimulation (3, 15, 30, 45, 60, and 90 minutes) and were assayed using Multiplex high sensitivity kits. Older adults had significantly higher biomarker concentrations at baseline ( $\beta$ -endorphin, Cortisol, Substance P, TNF- $\alpha$ , IL-6, IL-8, IL-4, IL-10,  $p$ 's<0.05). Most significantly, older adults had an earlier induction and delayed recovery of biomarkers compared to younger adults in response to pain ( $p$ 's<0.05), but not warm. ( $p$ <0.05). Our study is the first to show that even in healthy older adults; the immune and neuroendocrine response to pain is similar to the response in chronic pain patients. Our results also suggest that pain experiences, which are cumulative in aging, may be important contributors to the age-related imbalance in pro- and anti-inflammatory networks providing additional avenues for potential interventions.

**#13 TITLE: Effect of an aerobic exercise intervention on pain scores. A study design.**

**AUTHORS: Nathaniel R. Eckert, Warren H. Greenfield, Kelly M. Naugle, Yenisel Cruz-Almeida, Joseph L. Riley III**

Reports estimate that approximately 100 million U.S. adults experience some form of pain. This results in health care costs ranging \$560-635 billion annually through direct treatment and lost productivity. Recently, investigations have suggested that the implementation of chronic aerobic exercise reduces individual pain perception; providing a viable method of pain reduction therapy. However, the exact mechanisms of pain reduction associated with long-term aerobic exercise are unknown. Therefore the following study design seeks to elucidate the associated mechanisms of pain reduction through chronic aerobic exercise. Once eligible, subjects will undergo multiple, thorough pre-intervention pain testing sessions consisting of mechanical, thermal, cognitive, and cardiovascular measurements. This pre-intervention phase will then be followed up by a cardiovascular fitness assessment and exercise education session. The aerobic conditioning intervention will be designed to progressively increase the subject's aerobic capacity over a period of 8-10 weeks. Upon conclusion, the subject will return for thorough post-intervention pain testing allowing for comparison of pre-post pain testing scores. The data provided from this study will, for the first time, introduce a comprehensive investigation, looking at the mechanisms of pain reduction in chronic pain populations through the use of an individualized, long-term aerobic conditioning program. Such results will lead to further investigations on specific mechanisms allowing for the development of more specific and effective clinical pain therapies.

**#14 TITLE: Influence of testing modality on first, second, and temporal summation pain.**

**AUTHORS: Nathaniel R. Eckert, Genesis Nieves, Yenisel Cruz-Almeida, Chuck J. Vierck, Joseph L. Riley III**

Stimulus response curves (SRC) and temporal summation (TS) protocols typically employ the use of constant contact thermodes. "Tapping" devices are now also being used but comparisons across devices have not been demonstrated. Therefore, the purpose of this study was to investigate potential differences across modalities. 20 subjects (8 males; 24yrs±6) were tested at two different testing sites (Palm/Forearm) on the left arm with three different machines (PATH, TESS, TSAR). Testing included SRCs for both first and second pain, and TS trials. All pain ratings were recorded on an electronic pain scale of 0-100. Stimulation profiles elicited first and second pain, differing by stimulation duration (700ms vs. 2sec) and temperatures reached. TS temperature was determined as the temperature resulting in a 25±5 pain rating from SRC first pain scores. The SRC testing trials across machines demonstrated reliability in rating ( $r = 0.89-0.73$ ) suggesting reliable rating across trials and sites. TSAR SRC's produced the highest ratings followed by mixed results from the other modalities. Second pain SRC's demonstrated the greatest pain sensitivity and summation with the use of "tapping" machines. Results are difficult to determine with a lack of statistical power, most likely due to a small sample size, however a general consensus could be made suggesting that the use of the "tapping" machines results in a greater ability to evoke and measure first and second pain without the confounding variables present with constant contact machines. This result may be due to the amount of sensory information gained from a tapping thermode resulting in a slower rise in pain ratings, which may provide a better method of pain measurement and reliability when accounting for thermode size.

## #15 TITLE: Evidence for a central disorder of pain in PD and its relevance to PD cognition

**AUTHORS: Samantha Evans, Andrew Ahn, Jared Tanner, Catherine Price**

**Background:** Pain in Parkinson's disease (PD) has been attributed to the musculoskeletal complications of the movement disorder. Lacking definition are: 1) the neurological contributions to pain intensity and pain related disability, and, 2) relationships between pain and PD cognitive profiles.

**Methods:** From a federally funded investigation studying the neuroanatomical contribution to cognitive profiles of medicated non-demented individuals with idiopathic Parkinson's disease (PD;  $n=40$ ; UPDRS-III =17.60(10.73); age= 67.80(5.40)) and non-PD matched peers ( $n=40$ ; UPDRS-III=2.75(3.36), age=68.20(4.60)) we used the Brief Pain Inventory-Short Form (Cleeland, 1991) to examine hypotheses regarding 1) group differences in pain intensity versus pain disability and 2) associated neuroanatomical and cognitive associations. All individuals completed the same neuropsychological measures and structural brain magnetic resonance imaging protocol (3T, Siemens).

**Results:** PD had higher levels of pain-related disability (PD=11.40  $\pm$ 12.66); non-PD=3.98 $\pm$ 8.94;  $p<.01$ ) despite similar levels of pain intensity ( $p=.05$ ). Only for PD, pain ratings were negatively associated with thalamic volume (interference  $r = -0.45$ ,  $p<.01$ ; intensity  $r = -0.39$ ,  $p=.01$ ), with the amygdala associated only with pain interference (interference=-0.38,  $p=.02$ ; intensity  $r = -0.28$ ;  $p=.08$ ), and a trend for the putamen with intensity (interference= -0.22, $p=.16$ ; intensity  $r = -0.31$ ,  $p=.05$ ). Pain ratings were not associated with motor severity, but did increase with years of PD ( $r=0.41$ , $p<.01$ ). Only for PD, increased pain intensity associated with reduced processing speed ( $r=-0.38$ ,  $p=.02$ ) and inhibitory functions ( $r = -.36$ ,  $p=.03$ ).

**Conclusion:** Data show evidence for a central disorder of pain regulation in PD whose mechanisms may be distinct from the specific pathophysiology of the movement disorder. Pain was uniquely contraindicative for cognition in PD. Supported by NINDS K23NS060660 (CP); 1R01NS082386 (CP)

**#16 TITLE: Longitudinal assessment of connectivity across resting-state networks in a model of acute low back pain.**

**AUTHORS: C Gay, J Letzen, J Craggs, M Robinson, M Bishop**

**Aim of Investigation:** Patients with chronic low back pain (LBP) have demonstrated altered resting-state functional connectivity compared to pain-free controls. To extend these findings, we investigated whether acute LBP induces resting-state functional connectivity alterations. To do this, we applied similar resting-state methodologies in an experimental model of acute LBP and assessed the relationship among resting-state functional-network-connectivity (FNC) patterns, pain intensity, and pain sensitivity following the induction of delayed-onset muscle-soreness (DOMS).

**Methods:** Nineteen pain-free volunteers (mean age = 22.4, SD = 4.6, 74% female) completed an exercise paradigm to induce DOMS in the low back. Pain intensity (100-mm visual analog scale [VAS]), pressure pain thresholds over the low back (local) and extremities (remote), and FNC (correlation between network time-courses) were assessed twice: 1) prior to exercise and 2) 48 hours after exercise. Simple raw change scores (time2 – time1) were calculated for all measures. Five minutes and 42 seconds of resting-state fMRI data was collected at each time point and preprocessed using SPM12. Processed data was then entered into a group level independent component analysis (ICA) using the Group ICA of fMRI Toolbox to generate 20 components. Group components were spatially sorted using templates of four resting-state networks: the sensorimotor (SMN), executive control (ECN), salience (SN), and default mode (DMN). The group-level component for each network was then used to identify individual-level components for each network in both sessions. Change scores of connectivity among components' temporal waveforms (i.e., timecourses) were then estimated using the Functional Network Connectivity toolbox.

**Results:** Following the exercise paradigm, there was a mean LBP intensity increase of 10.9 (SD = 16.5),  $p=0.01$ , and a mean decrease in local pressure pain thresholds of 5.5 kg/

cm<sup>2</sup> (SD=6.7),  $p < 0.01$ . Remote pressure pain thresholds did not significantly decrease after exercise (mean = 0.5 kg/cm<sup>2</sup>, SD=4.1,  $p=0.6$ ). FNC results showed a general pattern of small increases in connectivity between all networks; however, these changes were not significant (SMN-ECN mean=0.05, SD=0.41,  $p=0.6$ ; SMN-SN mean=0.14, SD=0.37,  $p=0.12$ , SMN-DMN mean=0.01, SD=0.27,  $p=0.8$ , ECN-SN mean=0.03, SD=0.30,  $p=0.7$ , ECN-DMN mean=0.02, SD=0.23,  $p=0.7$ , SN-DMN mean=0.03, SD=0.34,  $p=0.7$ ). We did not find significant relationships in change scores across outcome domains, except for the change scores between SMN-DMN and remote pain sensitivity ( $r=-0.53$ ,  $p=0.02$ ).

**Conclusions:** Our findings suggest the exercise paradigm produces mildly intense acute LBP, with individual variation and local increases in pressure pain sensitivity. Further, in this model, we did not find an associated widespread increase in pressure pain sensitivity nor significant changes in functional connectivity across resting-state networks. This would suggest that the acute phase of LBP is not associated with the same resting-state (central nervous system) alterations that have been reported in the chronic phase of LBP. A logical next step would be to apply similar methodologies in a clinical population with acute low back pain. Limitations are noted, and further investigation is needed to improve the confidence in these results because of our relatively small sample size and the inherent problems in raw difference scores as a method for estimating change. None the less, this innovative use of DOMS as an experimental model permits studying clinically relevant pain and its mechanisms.

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**#17 TITLE: Exploring experience dependent changes in pain sensitivity using an exercise-induced injury as a model of acute low back pain**

**AUTHORS: Charles W. Gay DC, PhD; Mark D. Bishop PT PhD**

**Objectives:** The pain experience is assumed to be interrelated with measures of pain sensitivity. Our objective was to assess individual changes pain sensitivity based on their pain experience following an exercised-induced muscular-injury protocol and manual therapy. We hypothesize that individuals who experience pain would demonstrate greater pain sensitivity when compared to those who do not. Further, we suggest that individuals who have pain and then report improvement following manual therapy would show a reduction in pain sensitivity compared to individuals who do not experience improvement.

**Methods:** 92 subjects (mean age = 23.0,  $\pm$  4.6 years, 66.3% female) were randomized to complete an exercise-muscle-injury protocol or light exercise. The randomization schedule was 15 to 2. Post hoc groups were created based on subjects' reported pain experience. There were four a priori groups; control subjects (group 1, N=10), subjects who reported no low back pain (group 2, N=14), subjects who reported low back pain and had no pain-relief following MT (group 3, N=33), and subjects who reported low back pain and found relief following MT (group 4, N= 35). Pain sensitivity measures were taken 5 times, where baseline measures were taken prior to exercise-injury randomization. The four follow-up time points were: 48-hours following exercise and prior to MT; 48-hours following exercise and post MT; 72-hours following exercise; and 96-hours following exercise. Pain sensitivity was a composite of the following: pressure pain thresholds, pain intensity at pressure threshold, thermal threshold, thermal tolerance and supra-threshold pain ratings at 45°, 47°, 49° and 51°. Modality specific composite scores were also created for pressure sensitivity and heat sensitivity. Baseline data was used to create a mean and standard deviation for each pain sensitivity measures. The 5 time points of each measure were normalized using the same baseline mean

and standard. The single pain sensitivity was the average of all normalized individual scores. Mixed effects models, using restricted maximum likelihood, were used to test for differences between group (pain experienced) over the 5 time points, as well as temporal changes within groups and at each time point.

Results: Longitudinal changes in pain sensitivity were not dependent on the pain experience, (group-by-time-interaction, ( $F_{12, 269}=1.08$ ,  $p = 0.39$ ). However, when pain sensitivity was separated by modality, group-by-time-interactions were found for pressure ( $F_{12, 344} = 2.31$ ,  $p = 0.01$ ), but not thermal ( $F_{12, 346} = 1.71$ ,  $p = 0.06$ ). Decomposition of the pressure pain sensitivity interaction showed that the three groups who underwent the exercise-induced injury showed temporal variations in pain sensitivity (group 2,  $F_{4, 344} = 5.18$ ,  $p < 0.01$ ; group 3,  $F_{4, 344} = 5.09$ ,  $p < 0.01$ ; group 4,  $F_{4, 344} = 3.28$ ,  $p = 0.01$ ), while the control group did not ( $F_{4, 344} = 0.34$ ,  $p = 0.85$ ). For groups 2, 3 and 4, pressure pain sensitivity showed increases over time compared to the baseline time point.

Conclusion: Our findings did not support our hypothesis that longitudinal changes in pain sensitivity would be different in individuals who report pain versus those that did not. Further our findings do not support that pain sensitivity changes are dependent on whether or not an individual experiences improvement following a therapeutic intervention. We did find that compared to control subjects, individuals who underwent the exercise-induced muscle-injury protocol showed increases in pressure pain sensitivity overtime, which is similar to previous reports. Our findings also question the sensitivity to change in composite measures of pain sensitivity that are multi-modal (i.e., pressure and thermal).

**#18 TITLE: Salivary cortisol and fMRI-based measures of central sensitization following sham intervention for acute musculoskeletal pain**

**AUTHORS: Kara E Hannibal; Mark D Bishop**

Activity-dependent facilitation of glutamate-mediated excitatory postsynaptic potentials (EPSPs) and upregulation of brain-derived neurotrophic factor (BDNF) during central sensitization may augment synaptic plasticity and potentiate long-term neuroplastic alterations in pain circuitry. Cortisol secretion may facilitate persistent central sensitization and neuroplasticity by increasing glutamate and its NMDA receptors, prolonging calcium uptake, and upregulating BDNF and other neurotrophic factors. Similarly, cortisol secretion during an acute pain experience may potentiate neuroplastic alterations in pain circuitry that may underlie the transition from acute to chronic pain. This preliminary analysis investigates the relationship between cortisol and increases in central sensitization during a minor episode of acute musculoskeletal pain. Nine pain-free volunteers between 20-25 years old underwent a validated exercise protocol designed to induce delayed-onset muscle soreness (DOMS) to the lower back musculature. Central sensitization was assessed using fMRI during a common measure of temporal summation (TS), whereby repeated pulses of static suprathreshold heat were applied to the bottom of the right foot. Participants were told they would be randomized to 1 of 3 manual therapy interventions designed to treat low back pain. All participants received sham intervention, and central sensitization (TS during fMRI) was reassessed immediately thereafter. Salivary cortisol was collected immediately following fMRI scans. Overall, salivary cortisol concentration was associated with increases in hemodynamic responsiveness (HRF) in the pain processing regions of the brain during TS as compared to rest ( $p < .001$  FWE-corrected). Pre vs post intervention within groups analysis revealed associations between salivary cortisol and increases in HRF in the hypothalamus, hippocampus, basal ganglia, insula, and culmen following sham intervention ( $p < .001$  FWE-corrected). These findings provide preliminary evidence for the impact of cortisol on central sensitization, which

may represent the primary stages of neuroplasticity. Given the gene-mediated effects of cortisol on neuroplasticity, cortisol secretion during an acute pain experience may facilitate the transition to chronic pain.

## **#19 TITLE: Toward clinical decision support for chronic pain: integrating patient reported outcomes in an electronic health record**

**AUTHORS: Christopher Harle, PhD; Siegfried Schmidt, MD, PhD; Jonathan Shuster, PhD, Sean Mackey, MD, PhD; Alyson Listhaus, MPH; Lilliana Bell, MHA; Constanza Covarrubias, MPH; TaJuana Chisholm, MEd; Roger B. Fillingim, PhD Robert Hurley, MD, PhD**

Patients and clinicians frequently report dissatisfaction with primary care for chronic pain. Integrating pain-related Patient Reported Outcomes (PROs) in primary care practice could improve patient-clinician communication, satisfaction, and quality of care. However, prior research provides few examples of systems that effectively integrate PROs with electronic health records (EHRs). This study describes the technical design and implementation of a novel system for integrating PROs with an EHR to provide pain-related clinical decision support. This study is being conducted in primary care practices at the University of Florida. To collect PRO data at the point of care, we implemented the Collaborative Health Outcomes Information Registry (CHOIR) software developed at Stanford University. CHOIR provides a web-based computer interface through which patients can electronically complete computer-adaptive PRO assessments. In this study, we adapted CHOIR to comply with local security standards, align with primary care workflows, and administer thirteen PROs including: an interactive body map, pain intensity, pain catastrophizing, opioid risk, and nine pain-related PROMIS measures. After assessment, the system immediately and securely sends structured quantitative and qualitative results to the Epic EHR system for clinician review. Within the EHR, clinicians can review raw and standardized PRO scores and detailed responses to the PRO questionnaires. Also, clinicians can visualize PRO results over time and easily copy results in their notes. Our primary lessons learned in this study were the need to iteratively design and evaluate systems to ensure their fit with clinician and practice needs, the need to balance rigorous scientific evaluation with the pragmatic needs of primary care practices, and

the importance of close clinical, administrative, and informatics collaboration. In an ongoing clinical trial, we are evaluating the effect of the EHR-integrated CHOIR system on patient and clinician satisfaction with visits related to chronic pain.

Supported by a research grant from Pfizer, Inc.

## **#20 TITLE: Pain modulation profiles for patients with fibromyalgia and myofascial pain syndrome using REsponse-Dependent STIMulation**

**AUTHORS: Michael W. Havel, Corey B. Simon, Andre P. Mauderli, Joseph L. Riley III**

There has been recent recognition that laboratory pain research move away from measures of pain threshold and tolerance (shorter stimulus) to dynamic pain models that measure pain modulation (changes in pain sensitivity over time). We have recently developed a psychophysical model, REsponse-Dependent STIMulation (REDSTIM), which involves pain oscillating around a set point in response to ascending and descending temperature changes. Our work shows that REDSTIM establishes trends of sensitization following ascending series of stimulus intensities and desensitization following descending series. We propose that this provides an opportunity to separately evaluate inhibitory and facilitatory mechanisms of pain modulation. We present selected data from patients with Fibromyalgia and Myofascial Pain Syndrome in comparison with healthy controls using an intermittent-contact REDSTIM protocol to stimulate peripheral C-fibers. Subjects sit at an inclined desk and rate pain intensity by adjusting a sliding arrow on a 0-100 electronic visual analogue scale with pain ratings recorded in real time. The pre-heated thermode is recessed behind a cutout in a thermally neutral plastic surface, out of contact with the skin, which rests on the plastic surface. The thermode is brought into skin contact by a solenoid-powered mechanism for a 0.9-sec stimulus contact time with a 2.5-sec inter-stimulus-interval. Data from health controls show sine waves of heat with amplitude of 2-5°C and frequency of 8-15 seconds. Pain ratings generally follow in a similar pattern delayed by 3-6 seconds. Pain modulation profiles for patients vary considerably. Some generate profiles similar to controls; others show a slow response to heat intensity changes, whereas others exhibit extreme swings in pain ratings to small changes in temperature. These profiles types were classified with examples presented in figures. We also present test-retest data in 20 healthy controls across 4 sessions with inter correlations coefficients for profile parameters ranging from 0.75-0.96.

This study was funded in part by NIH Award R01AG039659.

**#21 TITLE: Pain and related symptoms reported by patients with chronic graft-versus-host disease and relationships among markers of inflammation and quality of life**

**AUTHORS: Debra Lynch Kelly, Debra E. Lyon, Suzanne Ameringer, John McCarty, Ronald K. Elswick**

Introduction: Chronic graft-versus-host disease (cGVHD) is a complex, multisystem complication affecting up to 40-70% of patients receiving allogeneic hematopoietic stem cell transplantation. It is the leading cause of non-relapse mortality in transplant survivors and may have a substantial impact on quality of life. The purpose of this study was to profile and examine the relationships among symptoms, peripheral markers of inflammation (selected cytokines and C-reactive protein), and quality of life (QoL). Understanding the characteristics of symptoms and biological correlates, such as inflammatory markers, is essential for the development of targeted clinical interventions leading to improved QoL.

Methods: Participants (n=24) were recruited from an urban health care center for this cross-sectional study. Relationships were examined using pairwise correlations. Symptoms were assessed using the Memorial Symptom Assessment Scale (MSAS), Brief Pain Inventory (BPI), Hospital Anxiety and Depression Scale (HADS), and Brief Fatigue Inventory (BFI). Cytokines levels were measured using the Bio-Plex<sup>®</sup> multiplex assay. C-reactive protein levels were measured using an enzyme-linked immunosorbant assay. QoL was assessed using the Functional Assessment of Cancer Therapy with a Bone Marrow Transplant sub-scale (FACT-BMT).

Results: Pain was reported by the majority (54%) of participants (noted on the BPI) and almost half (46%) reported activity interference due to pain. On a scale of 0 (no pain) to 10 (worst pain imaginable), scores ranged from 0 to 10 in this sample with a median score 5.8. There were significant relationships noted among pain, depression, and fatigue. Pain was found to be negatively correlated with QoL ( $r=.51$ ,  $p<.05$ ). Depression and fatigue were also negatively associated with QoL. The

MSAS identified pain as one of the most severe symptoms experienced among participants. No significant correlations were noted between pain and markers of inflammation in this sample; however Interleukin 6 was significantly different between individuals with and without fatigue regardless of cGVHD severity.

**Discussion and Conclusion:** This study profiles and examines the relationships among pain and other symptoms of cGVHD. Results add to the existing body of evidence suggesting pain is a common and distressing symptom experienced by individuals with cancer and is associated with other concurrent symptoms; however, under reported in this population. Understanding mechanisms influencing symptoms is important for the development of targeted interventions to mitigate pain and distressing symptoms and improve quality of life for transplant survivors with cGVHD.

**#22 TITLE: Changes in synovium and subchondral bone correlate with heightened limb sensitivity in a rat model of post-traumatic osteoarthritis**

**AUTHORS: Heidi E. Kloefkorn, Kyle D. Allen**

Purpose: Pain resulting from joint degeneration is the primary reason patients seek treatment for Osteoarthritis (OA), yet radiographic evidence of OA does not always correlate with patient reports of pain. This discrepancy can be explored in preclinical models of OA through detailed histological evaluation and behavioral assays. Most OA histological grading schemes focus on cartilage damage, however only weak correlations have been observed between these histological changes and pain-related behaviors. The purpose of this study is to describe new histological changes in a post-traumatic model of OA in a rodent and the associated between these changes and the development of pain-related behaviors.

Methods: OA was induced surgically by transecting the medial collateral ligament (MCL sham group, n=24) before exposing the joint and transecting the medial meniscus (MMT experimental group, n=24). At 2, 4, and 6 weeks post-surgery (n=16 at each week), mechanical sensitivity of the affected limb was assessed using von Frey filaments [Chaplan 1994]. After euthanasia, knees were collected and processed in paraffin for histological grading. Joint damage was assessed using the OARSI recommended histopathological grading scheme for the rat [Gerwin 2010]. In addition, subchondral bone ossification and synovial stroma cell morphology were assessed. Ossification of the deep zone cartilage was measured as the height and width of bone formed in the cartilage deep zone. Images of medial compartment synovial lining stroma were used to assess cell shape, size, and orientation. Data were assessed using ANOVAs with Tukey's HSD post-hoc tests and univariate linear correlations between histological changes and mechanical sensitivity.

Results: MMT rats exhibited progressive degeneration as measured by the OARSI scheme, but MCL sham animals were indistinguishable from naïve using this same scheme. However, both MMT and MCL sham animals

showed progressive ossification ( $p < 0.029$ ) and stroma cell morphology changes ( $p < 0.001$ ) relative to naïve animals. Moreover, femoral cartilage thickness ratio, ossification width, stroma cell alignment, and stroma cell aspect ratio all correlated significantly with limb sensitivity ( $p < 0.042$ ).

Conclusion: These additional histological measures are able to quantify non-cartilaginous changes, many of which correlate with heightened limb sensitivity, and distinguish MCL sham histological changes from naïve. By combining these measure with the OARSI recommended grading scheme, changes in all joint tissues can be considered during the assessment of OA models.

**#23 TITLE: Influences of pain self-efficacy on pain catastrophizing: evidence for mediation and moderation roles in outpatient orthopedic physical therapy**

**AUTHORS: Lentz TA, George SZ**

Self-efficacy is thought to instill resilience toward the negative effects of pain catastrophizing, however, has not been studied extensively in physical therapy settings. This study examined pain self-efficacy as a mediator and moderator of the relationship between pain catastrophizing and function, and pain catastrophizing and pain intensity. 394 patients with neck (22%), shoulder (24%), low back (29%) or knee (25%) pain completed the pain catastrophizing scale (PCS), pain self-efficacy questionnaire (PSEQ), numeric pain rating scale (NPRS), and SF-8 at initial physical therapy evaluation. Separate mediation analyses were performed for each dependent variable [SF-8 subscales (physical and mental) and NPRS], with PCS as the independent variable, and PSEQ as the mediator. Separate moderated regression analyses were performed for each dependent variable, with PSEQ as the moderator and age, sex, and socioeconomic status as covariates. Higher PCS scores were associated with lower SF-8 subscale scores, lower PSEQ scores, and higher pain intensity. Indirect effects (effect; 95% CI) confirmed that PSEQ mediated the relationships between PCS and SF-8 physical function (-0.20; 0.25 to -0.15), SF-8 mental function (-0.16; -0.22 to -0.11) and pain (0.03; 0.02 to 0.05). Significant direct effects of PCS in each model suggested only partial mediation. PSEQ moderated the relationship between PCS and SF-8 physical function only. In this model, the PSEQ x PCS interaction contributed an additional 1% [ $F(1,389) = 4.65$ ,  $p = .03$ ] to the final model. Compared to patients with low PSEQ scores, patients with high PSEQ scores showed stronger negative correlations between PCS scores and physical function. Pain catastrophizing may influence function and pain directly or through its relationship with pain self-efficacy. Psychologically-informed treatment approaches for improving physical function through reductions in pain catastrophizing may be most beneficial if low pain self-efficacy is addressed first. Prospective studies should confirm these benefits and establish temporal relationships among factors.

**#24 TITLE: Dysfunction of endogenous pain inhibition following acute aerobic exercise in healthy older adults**

**AUTHORS: Kelly M. Naugle, Keith E. Naugle, Joseph L. Riley III**

Laboratory based studies show that acute aerobic exercise reduces sensitivity to painful stimuli in young healthy individuals, indicative of a hypoalgesic response. However, little is known regarding the effect of aging on exercise-induced hypoalgesia (EIH) following aerobic exercise. The current study tested for differences between healthy older and younger adults in the magnitude of exercise-induced hypoalgesia of pressure and heat pain following moderate and vigorous aerobic exercise. Healthy younger (n=25) and older adults (n=18) completed one training session and three testing sessions consisting of 25 minutes of either vigorous (VAE) or moderate (MAE) intensity stationary cycling or quiet rest (control). The following measures were taken pre and post exercise/quiet rest: 1) pressure pain thresholds (PPT), 2) pain ratings (0-100 scale) during 30-sec of continuous noxious heat stimulation, and 3) pain ratings of 10 brief noxious heat pulses. Change scores were calculated for each condition (posttest – pretest). The control change scores were subtracted from the aerobic exercise change scores to determine the degree to which the outcome measures changed as a function of exercise (magnitude of EIH). Univariate repeated measures analyses compared the adjusted change scores between age groups. The results showed that the magnitude of EIH was significantly greater for younger compared to older adults following: 1) VAE for PPT (younger adults = +0.38kg ±0.1, older adults = -0.18kg ±0.1; p=.002), 2) VAE and MAE for pain ratings during prolonged noxious heat (VAE: younger adults = -4.8 ±2.4, older adults = +5.8 ±3.0; p=.001), and 3) VAE for pain ratings of repetitive noxious heat pulses (younger adults = -5.7±2.2, older adults = +8.2 ±2.9, p<.001). Generally, older adults showed no pain reduction or pain amplification following aerobic exercise. These results provide evidence for abnormal pain modulation following acute exercise in older adults.

**#25 TITLE: Associations between omega-6: omega-3 ratio, knee osteoarthritis pain and omega-3 supplementation**

**AUTHORS: Reddy D, Sibille KT, King C, Garrett T, Glover TL, Fillingim RB**

It is known that intake of omega-3 is associated with pain reduction in conditions such as rheumatoid arthritis, dysmenorrhea, inflammatory bowel disease, and neuropathy while high omega-6 levels are associated with inflammation and chronic pain. Also, there is good evidence that omega-3 levels increase with supplementation. The purpose of our study was to determine whether O6:O3 ratio was associated with pain and function in knee osteoarthritis (OA). We hypothesized that: 1) the O6:O3 ratio will be positively associated with knee (OA) pain and 2) a lower O6:O3 ratio will be associated with omega-3 supplementation. We also investigated demographic factors associated with supplementation. 168 individuals reporting knee pain completed self-report measures of knee pain including the Western Ontario and McMaster osteoarthritis index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), and Graded Chronic Pain Scale (GCPS). Blood samples were collected and evaluated for omega-6 and omega-3 levels, and the O6:O3 ratio was calculated. Findings indicate small but significant associations between the O6:O3 ratio and clinical pain and functioning, such that higher ratios are related to greater pain and disability. Also, individuals supplementing with omega-3 had lower O6:O3 ratios. Lastly, race/ethnicity, age, insurance status, and annual income were associated with O3 supplementation. These findings warrant further investigation. If associations of O6:O3 ratio and clinical symptoms are replicated, there may be benefit in determining whether omega-3 supplementation improves symptoms among individuals with knee OA.

**#26 TITLE: Monocytic cell responsiveness and estrogen-related influences on inflammation in TMD pain**

**AUTHORS: Ribeiro-Dasilva MC; Wallet S.M; Riley JL; Fillingim RB.**

**Objective:** The purpose of this study was to evaluate monocytic cell responsiveness and estrogen-related influences on inflammation in people with temporomandibular disorder (TMD) compared to controls. Also, the association between monocytic inflammatory response and self reported pain was evaluated in women with TMD.

**Methods:** Fourteen women with TMD pain and 13 healthy control participants completed a single clinic visit, which included a standardized clinical examination and assessment of self-reported pain, using the Graded Chronic Pain Scale. Baseline blood samples were taken and peripheral blood mononuclear cells were isolated and stimulated with LPS, with and without estrogen. For the statistical analyses, the mean score for current pain, worst pain, and average pain was computed. The statistical test included linear and logistic regression.

**Results:** TMD women exhibited a 4.5-fold greater IL-6 release after LPS ( $p=.003$ ) and 8-fold after LPS+estrogen stimulation compared to healthy controls ( $p=.005$ , for TMD group compared to healthy control group). Within the TMD group, women with more TMD severe self-reported pain in the VAS showed a 3.6-fold increase in IL-6 expression after LPS stimulation compared to baseline, while women with less severe self-reported pain had only a 2-fold increase of IL-6 after LPS stimulation compared to baseline with an ES=1.1. Pain ratings were correlated strongly with IL-6 at baseline, following LPS, and LPS+Estrogen ( $r=.61$ ,  $r=.50$ ,  $r=.53$ , respectively).

**Conclusion:** These findings suggest that individuals with TMD showed greater monocytic inflammatory responsiveness to LPS, which is further increased by stimulation with estrogen. Moreover, these monocytic inflammatory responses were positively associated with clinical pain levels. These results support the notion that TMD may be characterized by an estrogen-sensitive hyper-inflammatory phenotype.

**#27 TITLE: Comorbidities associated with patients attending an academic family medicine pain management program**

**AUTHORS: Michael Machek, MD, MSc; Lesa Gilbert, ARNP; George Samraj, MD; Alyson Listhaus, MPH; Siegfried Schmidt, MD, PhD**

Despite its prevalence, chronic pain is one of the most under treated and poorly understood conditions seen by primary care physicians. Comorbid conditions are seen amongst patients with various pain states. We introduced an innovative multidisciplinary pain management program into a residency based clinic to meet the needs of patients with chronic pain and to improve resident education. All patients enrolled in the program were screened for comorbidities such as depression, anxiety, panic attacks, substance abuse as well as alternative diagnosis, including fibromyalgia, medication-induced pain, and rheumatologic conditions. Physician and residents were able to determine most commonly encountered patient comorbidities of the first one hundred patients seen in the Chronic Pain Management at Main (CPM<sup>2</sup>) clinic. It was concluded that the most commonly associated non-pain related diagnoses associated with chronic pain visits were hypertension, tobacco use, and depression. The most common undiagnosed disorders found were Sacroiliac joint dysfunction, Myofascial Pain and Fibromyalgia. By identifying the various comorbidities in this patient population, their primary care physicians are better able to address previously unmanaged or poorly managed conditions that can contribute to worsening or uncontrolled chronic pain issues, such as hypertension and tobacco use. This pilot investigation supports that comorbid conditions may contribute to chronic pain. Identifying these conditions and effectively managing them is part of a good pain management. Family physicians with guidance and training can properly identify these conditions and treat them effectively. We also implemented using risk stratification measures to identify high risk patients not suitable for the primary care physicians practice. The risk stratification has been essential to provide safe pain management and refer high risk patients to specialty clinics.

**#28 TITLE: Establishing a pain management program within a university based family medicine residency**

**AUTHORS: Siegfried Schmidt, MD, PhD; Lesa Gilbert, ARNP; Ku-Lang Chang, M.D., Alyson Listhaus, MPH**

Chronic pain is one of the most frequent complaints presenting to family physicians, but both patients and family physicians report dissatisfaction with its care. Most residency programs provide minimal training in chronic pain management, which exacerbates this problem. There is a definite need for new curriculum to educate family medicine residents in the treatment of chronic pain. We will be describing our experience establishing a comprehensive and multidisciplinary pain management program since July 2013. The specific aim of this program is to improve the education of Family Medicine residents in the management of chronic pain and improve patient care through an evidence-based pain management model. The curriculum is based on the American Academy of Family Physician Recommended Curriculum Guidelines for Family Medicine Residents for Chronic Pain Management and using accepted principles in chronic pain management, such as Stepped Care to Optimize Pain Care effectiveness (SCOPE) principles. Our residents have significant difficulties managing their own patients with this problem; we decided to establish this program within the Family Medicine Residency Program clinic at the University of Florida.

**#29 TITLE: Evaluation of the first 100 patients at chronic pain management program at main (CPM2)**

**AUTHORS: Siegfried Schmidt, MD, PhD; Lesa Gilbert, ARNP; Alyson Listhaus, MPH; George Samraj, MD**

Chronic pain affects more than 100 million people and is the most expensive public health problem in the U.S. We will be describing our experiences establishing a comprehensive and multidisciplinary pain management program in the Family Medicine Residency Program at the University of Florida since July 2013. The program aims to provide safe and effective pain management to underserved, vulnerable patients with complex medical problems. The Residency Program trains family medicine residents (10 residents per year), and medical and pharmacy students. It has about 50,000 patient visits per year. Our patients have multiple barriers for access to pain management due to their complex biopsychosocial problems. We evaluated demographic and clinical information for the first 100 patients at the CPM2. Patients are predominately white (67%), females (57%), with Medicaid as their primary payer (47%), and are between the ages of 45-64 (64%). The first 100 patients had 492 visits between 7/2/2013 and 4/14/2015. The comparison of medication prescribed in the month prior to their first CPM2 visit and the month after their visit showed changes, such as a reduction in opioids, and benzodiazepines, but also an increase in antidepressants. Additionally, we evaluated risk of opioid-related aberrant behavior by the use of the Opioid Risk Tool (ORT) and assessed drug screens stratified by ORT score.

**#30 TITLE: Placebo analgesia enhances descending pain-related effective connectivity: a dynamic causal modeling study of endogenous pain modulation**

**AUTHORS: Landrew S. Sevel, M.S., Jason G. Craggs, Ph.D., Donald D. Price, Ph.D., Roland Staud, M.D., and Michael E. Robinson, Ph.D.**

The use of placebo to reduce pain is well documented; however, knowledge of the neural mechanisms underlying placebo analgesia (PA) remains incomplete. This study used fMRI data from 30 healthy subjects, and dynamic causal modeling (DCM) to investigate changes in effective connectivity associated with the placebo analgesic response. Before scanning, subjects were conditioned to expect less thermal pain at 2-of-4 sites on their feet. VAS pain ratings revealed a significant but small difference between the baseline and placebo sites [mean difference = 6.63,  $t(29) = 3.91$ ,  $p \leq 0.001$ ,  $d = 0.97$ ], confirming an analgesic effect. However, no significant differences in magnitude of brain activation between conditions were observed via traditional random effects general linear modeling. DCM was then used to investigate changes in effective connectivity during PA. The results indicate that during the PA but not baseline condition, the couplings between brain regions including those involved in cognitive processes (e.g., attention, expectation, and evaluation) were significantly enhanced. Specifically, a significantly consistent decrease in the DLPFC->PAG coupling was found. These findings highlight the differences between pain processing and modulation at the network level. Moreover, our results suggest that small placebo effects may be better characterized via changes in the temporal dynamics among pain modulatory regions rather than only changes in the magnitude of BOLD activation. Further application of nuanced analytical approaches that are sensitive to temporal dynamics of pain-related processes such as DCM are necessary to better understand the neural mechanisms underlying pain processing in patient populations.

**#31 TITLE: Optimizing chronic pain treatment with enhanced neuroplastic responsiveness**

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Neuroimaging findings demonstrate that chronic pain is associated with short and long-term changes in the brain. Recent advances indicate promising opportunities to “re-open” and enhance neuroplastic responsiveness with non-pharmacological, non-invasive strategies such as food restriction. Additionally, extensive evidence suggests that glucose administration, strategically implemented, promotes enhanced learning and memory. Strategies to maximize neuroplastic responsiveness to chronic pain treatment could enhance treatment gains by accelerating neurogenesis and increasing learning and positive central nervous system (CNS) adaptation. The proposed study endeavors to identify strategies designed to optimize the neurobiological environment to respond to clinical treatment interventions and override the maladaptive neuroplastic changes associated with chronic pain. The overall aims are to: 1) determine whether food restriction and/or glucose administration will enhance neuroplastic responsiveness and improve learning retention thereby improving the effectiveness of guided imagery intervention in chronic pain patients; 2) identify neurobiological and biological mechanisms underlying the proposed interventions. Sixty adults with osteoarthritis-related chronic pain will be randomized to one of three groups: food restriction, glucose administration, or placebo and will participate in a 3 week intervention. The study will generate pilot data with a goal of identifying strategies to optimize pain treatment outcomes by applying non-invasive approaches to augment neuroplasticity.

**#32 TITLE: Central pain processing measures are associated with movement-evoked pain report among older adults with chronic axial low back pain**

**AUTHORS: Corey B. Simon, Mark D. Bishop, Joseph L. Riley III, Roger B. Fillingim, Steven Z. George**

Research has been slow to elucidate associations between chronic low back pain (CLBP) and neuroplastic pain processing changes. One problem is previous studies have relied on spontaneous pain measures (e.g. resting pain) rather than evoked pain measures which may be more attributable to musculoskeletal conditions (e.g. movement-evoked pain). Moreover, age-related pain processing changes have been reported among healthy individuals, yet not examined among individuals with CLBP. In this study, CLBP individuals underwent a comprehensive battery of pain processing measures over 4 sessions. Associations between spontaneous pain (resting, daily), evoked pain (movement), and pain processing (e.g. threshold, summation, aftersensations) were compared. Overall, pain processing comprised ~20% of the variance in movement-evoked pain intensity compared to 4-9% in spontaneous pain intensity. After accounting for demographic risk factors (e.g. self-rated health, education), pain processing was not associated with spontaneous pain ( $p > .05$ ). However, multiple pain processing measures were positively associated with movement-evoked pain ( $R^2 = .10-.13$ ,  $p < .01$ ). These associations were then compared across younger (18-39 years;  $n=20$ ), middle-aged (40-56 years;  $n=20$ ) and older (57-76 years;  $n=20$ ) age groups. Pain processing was not associated with movement-evoked pain among younger adults, however, explained 6-16% of the variance among middle-aged adults and ~28% of the variance among older adults. Findings suggest that laboratory correlates of pain processing are not associated with spontaneous pain; however, may play an important role in movement-evoked pain. Further, the influence of pain processing on movement-evoked pain may increase with age. Future research will elucidate the extent to which pain processing predicts CLBP, and whether decrements in pain processing increase the predisposition and/or maintenance of CLBP among older adults.

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**#33 TITLE: Effect of spinal manipulations and body-based interventions in a model of experimentally induced low back pain**

**AUTHORS: Solis, FM., Bishop, MD.**

This study evaluated the effect of manipulative and body-based interventions (MBB) on low back pain (LBP) using an experimental model, and the association between pressure pain threshold (PPT) and body area of pain distribution. Sixty pain-free volunteers ( $F=42$ ,  $Age=22.7\pm 4$  y/o) were tested at 5 time points. The experimental pain model was implemented at baseline using delayed onset muscle soreness (DOMS). Two days later a MBB (spinal manipulation, mobilization or touch control) was performed. This is a preliminary analysis of an ongoing RCT and therefore all data were analyzed together. Patients rated their pain at the moment of testing using the numeric rating scale (0=no pain, 100=worst pain imaginable). PPT was assessed bilaterally at T12, L5 and S2. Subjects also shaded the body area that was painful at the moment of testing using a body pain diagram and then quantified in mm<sup>2</sup>. Paired sample T-test evaluated the effect of DOMS induction. Repeated-measure ANOVA examined the effect of the interventions over time. Pearson's correlation determined the association between PPT and painful body area. After DOMS pain increased from  $1\pm 2.8$  to  $12.9\pm 15.6$  ( $p<0.001$ ), body area of pain distribution from  $9.2\pm 38.4$  to  $103.5\pm 215$  mm<sup>2</sup> ( $p=0.001$ ) and PPT decreased from  $21.4\pm 9.5$  to  $18.1\pm 9$  kg ( $p<0.001$ ). LBP decreased after MBB interventions from  $12.9\pm 15.6$  to  $4.8\pm 7.3$  ( $p=0.003$ ) on the intervention day. Body area of pain distribution decreased 24 hours after the treatment from  $103.5\pm 215$  to  $49.9\pm 113$  mm<sup>2</sup> ( $p=0.04$ ) and continue to decrease 48 hours later to  $23.8\pm 23.8$  mm<sup>2</sup> ( $p=0.003$ ). Body area was negatively associated with PPT before ( $r=-0.310$ ,  $p=0.018$ ) and 24 hours after intervention ( $r=-0.305$ ,  $p=0.020$ ). MBB interventions have an immediate effect on decreasing pain intensity and body area in a model of acutely induced muscular LBP. This study suggests that the changes observed in the discriminative aspects of pain sensations are centrally and not peripherally mediated.

**#34 TITLE: Role of participant expectations in clinical outcomes in subjects with neck pain**

**AUTHORS: Fredy Solis, Mark Bishop, Joel Bialosky**

Neck pain is significant cause of global disability necessitating effective interventions. Multiple impulse therapy (MIT) is a mechanical manual therapy device supported by preliminary studies as effective in resolving neck pain. This study investigated the efficacy of MIT for improving pain and function in participants with neck pain and examined the influence of participant expectations. Fifty-eight participants (age=34±13 y/o) with neck pain (duration=181±289 w) were randomized to MIT, cranio-cervical flexion exercises (CCF), or control group. Participants in the intervention groups received their assigned intervention for 6 sessions over 2 weeks while the control group was followed over 2 weeks and served as a natural history comparator. All participants underwent baseline and follow up testing at 2 weeks. Function was assessed with the neck disability index (NDI) and clinical pain with a visual analog scale (VAS). Participants receiving MIT or CCF indicated on separate VAS their expectations for MIT and CCE to improve their neck pain. Participants were categorized as responding or not to their assigned intervention based upon 30% improvement in function and pain. More responders were present in the MIT group (82.4%) compared to the CCF group (42.1%) and control group (47.1%) for pain  $\chi^2=6.85$ ,  $p=0.03$  however group differences were not observed in responders based on function ( $p=0.83$ ). A trend was observed ( $p=0.09$ ) for more participants being characterized as treatment responders based on functional improvements when matched to the treatment for which they expressed greater expectation (81.3%) than those not matched (52.9%). Pain decreased whether participants received treatment for which they had higher expectations or not ( $p=0.62$ ). These findings are consistent with other manual therapy studies indicating an influence of expectation on outcomes. Our findings suggest that expectations have a greater influence on function than pain in individuals with neck pain.

**#35 TITLE: Finding good TEMPOS with the SAX: preliminary definitions of temporal postoperative pain signatures via symbolic aggregate approximation**

**AUTHORS: Tighe PJ, Rashidi P, Nickerson P, Fillingim R**

Introduction: Severe acute postoperative pain afflicts up to 60% of surgical patients.<sup>1</sup> Recent data from Chapman and Althaus suggests that over one-third of surgical patients have sustained, or even increasing, pain scores on postoperative days one through six, and that the slope of this linear trajectory is associated with the development of persistent postsurgical pain.<sup>2,3</sup> However, these reports relied upon daily pain assessments and thus were unable to examine within-day fluctuations of pain intensity ratings. Here, we use symbolic aggregate approximation (SAX) pain data in order to derive distinct phenotypes of temporal postoperative pain signatures (TEMPOS).

Methods: This retrospective cohort study was approved by the Institutional Review Board (IRB-01) at the University of Florida. We examined over 400,000 pain scores from over 8,000 adult patients who received non-ambulatory surgery over a one-year period at the University of Florida. Pain scores were collected as part of routine nursing assessment on postoperative days 0-7 using a time-stamped numerical rating scale. Given the large set of pain assessments, customary approaches to processing time series data include k-NN and dynamic time warping which lead to prohibitive computational times, and so we employed SAX to identify distinct temporal signatures (motifs) used for defining preliminary measures of TEMPOS.<sup>4</sup>

Results: In these preliminary results, TEMPOS were visualized via intelligent icons created for different types of surgery defined by anatomic location.<sup>5</sup> Figure 1 demonstrates these intelligent icons for each category of surgery, ranked by their similarity to cardiovascular surgery. Similarities in the TEMPOS between each type of surgery were subsequently measured using cosine similarity.<sup>6</sup> The similarity in TEMPOS between each type of surgery is measured along the interval of  $[-1, 1]$  with 1 indicating an exact match and -1 reflecting absolute

discordance. Cardiovascular and pulmonary types of surgery had the greatest cosine similarity in TEMPOS at 0.598. Contrariwise, female genital and cardiovascular surgery had the greatest cosine dissimilarity in TEMPOS at -0.661. Table 1 demonstrates the similarities in TEMPOS between different types of surgery.

Conclusion: Our preliminary implementation of motif representation using SAX identified distinct TEMPOS across different types of surgery defined by anatomic location. Additional studies already underway will consider the impact of sociodemographic dimensions on TEMPOS. Further work is needed needed to both better refine TEMPOS definitions and determine their contribution to both acute and chronic pain outcomes as well as global assessments of surgical recovery.

**#36 TITLE: Is acute pain medicine ready for Markov? Preliminary testing of sequential postoperative pain intensity transition matrix stabilities**

**AUTHORS: Nicholas Wright, Haldun Aytug, Roger B. Fillingim, Patrick J. Tighe**

**Introduction:** Chapman and others have previously demonstrated the importance of postoperative pain trajectories. Markovian modeling methods may permit the sequential consideration of the pain state, analgesic intervention, and the functional capacity to guide sequential clinical decision making. To identify a suitable Markovian model, we tested the hypothesis that the conditional probability distributions of pain state transitions remain stable over sequential postoperative pain intensity assessments.

**Methods:** The University of Florida IRB approved this study. We examined the first five clinically recorded postoperative pain intensity ratings from a mixed surgical cohort of 26,090 patients. Using a probabilistic graphical model, we then measured the probability that a patient would transition from a given pain intensity rating to a subsequent pain intensity rating between each of the first four transition steps.

**Results:** In our cohort, 51.1% of subjects were female; 22.5% were  $\leq 44$ , 47.4%  $\leq 66$ , 28.9%  $\leq 88$ , and 1.3%  $> 88$ . For initial pain states, zero was the most likely initial pain score across all age and sex stratifications (range 30.7%–74.6%; Table 1). Sequential transition matrices demonstrated high probabilities for all pain states to 0, and 10 to 10 for all four matrices. Additional trends were noted with high proportions of transitions to 0 from any pain state, as well as transitioning to the same pain state (Table 2).

**Conclusions:** Our results suggest clinically measured postoperative pain intensity rating state transitions exhibit stable conditional probability distribution over the first five pain assessments, suggesting Markovian methods may be feasible in describing postoperative pain state changes.

**#37 TITLE: When does postoperative pain resolve? Differences in time to onset of durable effective acute postoperative pain relief (DEAPPR)**

**AUTHORS: Patrick J. Tighe, MD, MS, Christopher D. King, PhD, Baiming Zou, PhD, and Roger B. Fillingim, PhD**

**Introduction:** Prior work on postoperative pain trajectories have examined pain score changes over time using daily averages of pain scores. However, little is known about the time required until patients consistently report minimal postoperative pain.

**Methods:** This study was approved by the local IRB. We conducted a retrospective cohort study of surgical case data from 7,293 adult patients to examine the impact of age, gender, and the type of surgery on the time to durable effective acute postoperative pain relief (DEAPPR). We defined DEAPPR as the time required until a patient reports the first of multiple (2, 3, 4, or 5 sequential measurements; e.g., DEAPPR-2, DEAPPR-3, etc.), uninterrupted, mild pain scores ( $\leq 4/10$ ).

**Results:** Overall, DEAPPR times ranged from 3 min for DEAPPR-2 and 9 min for DEAPPR-5 to 160.1 h for DEAPPR-2 and 183.1 h for DEAPPR-5. For the DEAPPR-2 outcome, the median time to event was 10.9 h (interquartile range [IQR], 3–26.1 h) after surgery. For the DEAPPR-5 outcomes, the median time to event was 31.5 h (IQR, 17.8–54.2 h) after surgery. This peak median difference between two sequential DEAPPR definitions was between DEAPPR-3 and DEAPPR-2 at 9 h, with subsequent decreases to 6.5 h between DEAPPR-4 and DEAPPR-3, and 5.2 h between DEAPPR-5 and DEAPPR-4. There were statistically different differences across DEAPPR 2-5 definitions by age, gender, and type of surgery.

**Conclusions:** Although additional analyses are necessary, DEAPPR may represent a novel method for evaluating acute pain service performance.

**#38 TITLE: Experimental pain phenotyping in older adults with knee osteoarthritis**

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Pain associated with knee osteoarthritis (OA) represents a significant source of disability in older adults, and recent evidence demonstrates enhanced experimental pain sensitivity among individuals with OA. Previous research has demonstrated considerable heterogeneity in the OA clinical pain presentation. However, less is known regarding the variability in responses to experimental pain in this population. The present study examined patterns of responses to a multimodal experimental pain battery and their relationship to demographic and psychosocial variables in older adults with knee OA. Individuals with knee OA (n=292) who participated in the Understanding Pain and Limitations in Osteoarthritic Disease (UPLOAD) study completed demographic and psychological questionnaires followed by a quantitative sensory testing (QST) session. QST measures were subjected to variable reduction procedures to derive pain sensitivity index (PSI) scores, which in turn were entered into a cluster analysis. PSI scores were derived for heat temporal summation, heat pain, pressure pain, cold pain and punctate mechanical temporal summation. Five clusters were significantly different across all pain index variables ( $p < 0.001$ ). Specifically, clusters were characterized by low pressure pain sensitivity, high pressure pain sensitivity, high punctate pain sensitivity, high heat pain sensitivity and base level sensitivity. Clusters differed significantly by race, gender, somatic reactivity, pain coping strategy catastrophizing and measures of clinical pain. The most robust differences across all variables were observed

between the least pressure pain sensitive cluster and the cluster characterized by increased sensitivity to heat pain. This study supports the notion that there are distinct subgroups or phenotypes based on experimental pain sensitivity in adults with knee OA, which in turn supports past findings of similar cluster characterizations in healthy adults. Future research is needed to further understand the pathophysiological mechanisms underlying the clinical pain within these subgroups, which may be of further value in tailoring effective treatments for this population.