

# The Journal of Pain

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### REVIEW ARTICLE

#### **643 A Systematic Review and Meta-Analysis of the Association Between Perceived Injustice and Depression**

Julie Lynch, Susan Fox, Paul D'Alton, and Keith Gaynor

Perceived injustice is increasingly recognized as a risk factor for problematic recovery, with a growing body of evidence documenting its association with heightened pain, disability, medication use, anger and post-traumatic stress. The aim of this paper was to systematically review and critically appraise the association between perceived injustice and depressive symptomatology across a wide range of medical and mental health populations. Results indicated a moderate to strong positive association, and the clinical implications are discussed. These findings could help clinicians in the field of pain and rehabilitation identify who may be at greater risk for a problematic recovery trajectory.

### ORIGINAL REPORTS

#### **655 Optimization of Spinal Manipulative Therapy Protocols: A Factorial Randomized Trial Within a Multiphase Optimization Framework**

Julie M. Fritz, Jason Sharpe, Tom Greene, Elizabeth Lane, Maliheh Hadizadeh, Molly McFadden, Douglas Santillo, Jedidiah Farley, Jake Magel, Anne Thackeray, and Gregory Kawchuk

Spinal manipulative therapy (SMT) is a common nonpharmacologic treatment for low back pain (LBP). Although generally supported by systematic reviews and practice guidelines, clinical trials evaluating SMT have been characterized by small effect sizes. This study adopted a multiphase optimization strategy framework to examine SMT protocol among 241 participants. All subjects received 2 treatment sessions the first week, then were randomly assigned additional treatments based

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#### ON THE COVER

The protease activated receptor (PAR) family is a group of G-protein coupled receptors activated by proteolytic cleavage of the extracellular domain. PARs are expressed in a variety of cell types with crucial roles in hemostasis, immune responses, inflammation, and pain. PAR3 is the least researched of the four PARs. This work aimed to better understand its potential function in the peripheral sensory nervous system by evaluating the role of PAR3, a G-protein coupled receptor, in nociception by developing a selective peptide agonist. These results suggest that PAR3 contributes to nociception in various contexts and plays a role in modulating the activity of other PARs. See Mwirigi, et al, Page 692.

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on a factorial design. Differing co-interventions with mechanistic and patient-centered outcomes were included. Patient-centered outcomes were optimized by inclusion of lumbar multifidus strengthening exercises, findings show.

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### **Sensory and Psychological Factors Predict Exercise-Induced Shoulder Injury Responses in a High-Risk Phenotype Cohort**

Katie A. Butera, Mark D. Bishop, Warren H. GreenfieldIII, Roland Staud, Margaret R. Wallace, Paul A. Borsa, Roger B. Fillingim, and Steven Z. George

This team's prior research identified a high-risk phenotype (high pain sensitivity variant of the catechol-O-methyltransferase gene) and pain catastrophizing scores for shoulder pain. This study identified sensory and psychological predictors of heightened pain responses following exercise-induced shoulder injury. Movement-evoked pain, pain intensity, disability, and strength were assessed 24 hours post-injury. Demographic, sensory, and psychological variables were included as predictors in full and parsimonious models for each outcome. Findings indicate specific pain sensitivity and psychological measures may have additional prognostic value for self-reported disability within a high-risk phenotype. These results should be tested in a clinical cohort for validation

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### **Modifications in fMRI Representation of Mental Rotation Following a 6 Week Graded Motor Imagery Training in Chronic CRPS Patients**

Sebastian Strauss, Silke Barby, Jonas Härtner, Nicola Neumann, G. Lorimer Moseley, and Martin Lotze

Complex regional pain syndrome (CRPS) is a neuropathic pain condition that is difficult to treat. For behavioral interventions, graded motor imagery (GMI) showed relevant effects, but underlying neural substrates in patient groups have not been investigated. A previous study investigating differences in the representation of a left/right hand judgment task demonstrated less recruitment of subcortical structures, such as the putamen, in CRPS patients than in healthy controls. To test for longitudinal effects of GMI training, researchers investigated 20 CRPS patients in a wait-list crossover design with 3 evaluation time points. Patients underwent a 6 week GMI treatment and a 6 week waiting period in a randomized group assignment and treatment groups were evaluated by a blinded rater. When compared to healthy matched controls at baseline, CRPS patients showed less functional activation in areas processing visual input, left sensorimotor cortex, and right putamen. This study presents the first longitudinal intervention study on CRPS patients testing functional representation of mental rotation of hands using a fMRI hand lateralization paradigm.

**692 A Role for Protease Activated Receptor Type 3 (PAR3) in Nociception Demonstrated Through Development of a Novel Peptide Agonist**

Juliet Mwirigi, Moeno Kume, Shayne N. Hassler, Ayesha Ahmad, Pradipta R. Ray, Changyu Jiang, Alexander Chamessian, Nakleh Mseeh, Brea P. Ludwig, Benjamin D. Rivera, Marvin T. Nieman, Thomas Van de Ven, Ru-Rong Ji, Gregory Dussor, Scott Boitano, Josef Vagner, and Theodore J. Price

The protease activated receptor (PAR) family is a group of G-protein coupled receptors activated by proteolytic cleavage of the extracellular domain. PARs are expressed in a variety of cell types with crucial roles in hemostasis, immune responses, inflammation, and pain. PAR3 is the least researched of the four PARs. This work aimed to better understand its potential function in the peripheral sensory nervous system by evaluating the role of PAR3, a G-protein coupled receptor, in nociception by developing a selective peptide agonist. These results suggest that PAR3 contributes to nociception in various contexts and plays a role in modulating the activity of other PARs.

**707 Exposure to an Immersive Virtual Reality Environment can Modulate Perceptual Correlates of Endogenous Analgesia and Central Sensitization in Healthy Volunteers**

Erzsebet Mehesz, Hajer Karoui, Paul H. Strutton, and Sam W. Hughes

Virtual reality (VR) has been shown to produce analgesic effects during experimental and clinical pain states. Yet, the top-down mechanisms are still poorly understood. This study examined the influence of both a real and sham (i.e., the same images in 2D) immersive arctic VR environment on conditioned pain modulation (CPM) and in a human surrogate model of central sensitization in 38 healthy volunteers. CPM and acute heat pain thresholds were assessed before and during VR/sham exposure in the absence of any sensitization. Findings show that exposure to an immersive VR environment can modulate perceptual correlates of endogenous pain modulation and secondary hyperalgesia. Results suggest that VR could provide a novel mechanism driven analgesic strategy in patients with altered central pain processing.

**715 Serotonin Plays a Key Role in the Development of Opioid-Induced Hyperalgesia in Mice**

Mika Sasaki, Yoshinori Kamiya, Keiko Bamba, Takeshi Onishi, Keiichiro Matsuda, Tatsuro Kohno, Miyuki Kurabe, Kenta Furutani, and Harue Yanagimura

Opioid usage for pain therapy is limited by its undesirable clinical effects, including paradoxical hyperalgesia, also known as opioid-induced hyperalgesia, (OIH). However, mechanisms associated with the development and maintenance of OIH remain unclear. This work investigated the effect of serotonin inhibition by the 5-HT<sub>3</sub> receptor antagonist, ondansetron, as well as serotonin deprivation via its synthesis inhibitor para-chlorophenylalanine, on mouse OIH models, with

particular focus on astrocyte activation. This study revealed that the descending serotonergic pain-facilitatory system in the spinal dorsal horn is crucial in OIH, and that activation of astrocytes is a secondary phenotype of OIH. The results offer new therapeutic targets for OIH and may help reduce inappropriate opioid use.

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**Desire to Receive More Pain Treatment – A Relevant Patient-Reported Outcome Measure to Assess Quality of Post-Operative Pain Management? Results From 79,996 Patients Enrolled in the Pain Registry QUIPS from 2016 to 2019**

Marcus Komann, Philipp Baumbach, Ulrike M. Stamer, Claudia Weinmann, Christin Arnold, Esther Pogatzki-Zahn, and Winfried Meißner

Acute postoperative pain is frequently evaluated by pain intensity scores. However, interpretation of the results is difficult and thresholds requiring treatment are not well defined. Additional patient-reported outcome measures (PROMs) might be helpful to better understand individual pain experience and quality of pain management after surgery. We used data from The Quality of Postoperative Pain registry (QUIPS) for a cross-sectional study in order to investigate associations between the desire to receive more pain treatment (D2RMPT) with pain intensity ratings and other PROMs. Responses from 79,996 patients were analyzed, of whom 10.7% reported D2RMPT. This measure could be used to apply pain treatment in a more individualized way and lead to improved treatment strategies and quality.

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**Gray Matter Brain Alterations in Temporomandibular Disorder Tested in a Population Cohort and Three Clinical Samples**

Martin Domin, Nikolai K. Grimm, Kai Klepzig, Carsten O. Schmidt, Bernd Kordass, and Martin Lotze

Temporomandibular pain (TMD) is a frequent symptom comprising pain around the mandibular jaw with a high dependence on stressors. Chronic pain has been associated with changes of the brains grey matter volume (GMV), but previous studies on GMV alterations associated with TMD have yielded contradictory results. This study tested GMV alterations using voxel based morphometry in three clinical samples and a population sample with 57 participants who indicated facial pain for the last 6 months. The GMV of pain patients was compared against age-matched and gender-matched participants without chronic pain who underwent the same assessments as the patient group. In a region of interest analysis, only the clinical samples showed an effect of decreased GMV for the anterior medial cingulate cortex reaching into the medial prefrontal cortex, known to be especially vulnerable for chronic pain grey matter volume reduction. Overall, an important question remains as to whether most inconsistent results from VBM-studies in chronic pain are related to chance results facilitated by small sample size and selection of patient samples.

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**Imprecise Visual Feedback About Hand Location Increases a Classically Conditioned Pain Expectancy Effect**

Thais Cristina Chaves, Tasha R. Stanton, Ashley Grant, Brian W. Pulling, Victoria J. Madden, Roger Newport, and G. Lorimer Moseley

This research tested the hypotheses that rendering sensory input about imprecise hand location increases a classically conditioned pain expectancy effect, and increases generalization of the effect to novel locations and reduces extinction of the effect. Forty participants underwent a differential classical conditioning experiment; subjects were not aware of the real aim of the study. Participants were randomly allocated to an Imprecise group (vision was disrupted to right or left) or a Precise group (vision was not disrupted). Conditioned pain expectancy was greater when sensory information about location was less precise. This adds support to the possibility that associative learning may play a role in the progression of an acute pain episode to a more generalized pain disorder.