MEAGAN E. ITA, MS<sup>1</sup> • SIJIA ZHANG, BS<sup>1</sup> • TIMOTHY P. HOLSGROVE, PhD<sup>1</sup> SONIA KARTHA, BS<sup>1</sup> • BETH A. WINKELSTEIN, PhD<sup>1,2</sup>

# The Physiological Basis of Cervical Facet-Mediated Persistent Pain: Basic Science and Clinical Challenges

eck pain is common and has emerged as a worldwide leading contributor to years lived with disability over the past 2 decades.<sup>102</sup> Neck pain often becomes chronic, with a 12-month prevalence ranging from 30% to 50%.<sup>34</sup> Moreover, individuals who have worsening neck pain also show poor measures of health-related quality of life.<sup>63</sup> At each spinal level from the cervical to the lumbar spine, there are bilateral

synovial facet joints between adjoining vertebrae. In the cervical spine, these joints are a common source of neck pain and are susceptible to injury from trauma or during spinal degenera-

• SYNOPSIS: Chronic neck pain is a common condition and a primary clinical symptom of whiplash and other spinal injuries. Loading-induced neck injuries produce abnormal kinematics between the vertebrae, with the potential to injure facet joints and the afferent fibers that innervate the specific joint tissues, including the capsular ligament. Mechanoreceptive and nociceptive afferents that innervate the facet have their peripheral terminals in the capsule, cell bodies in the dorsal root ganglia, and terminal processes in the spinal cord. As such, biomechanical loading of these afferents can initiate nociceptive signaling in the peripheral and central nervous systems. Their activation depends on the local mechanical environment of the joint and encodes the neural processes that initiate pain and lead to its persistence. This commentary reviews the complex anatomical, biomechanical, and physiological consequences of facet-mediated whiplash injury and pain. The clinical presentation of

tion.<sup>34,41</sup> The abnormal kinematics that are produced in the spine during a whiplash exposure or other dynamic spine loading can injure the individual tissues in the facet joint and/or the joint as a

facet-mediated pain is complex in its sensory and emotional components. Yet, human studies are limited in their ability to elucidate the physiological mechanisms by which abnormal facet loading leads to pain. Over the past decade, however, in vivo models of cervical facet injury that reproduce clinical pain symptoms have been developed and used to define the complicated and multifaceted electrophysiological, inflammatory, and nociceptive signaling cascades that are involved in the pathophysiology of whiplash facet pain. Integrating the whiplash-like mechanics in vivo and in vitro allows transmission of pathophysiological mechanisms across scales, with the hope of informing clinical management. Yet, despite these advances, many challenges remain. This commentary further describes and highlights such challenges. J Orthop Sports Phys Ther 2017;47(7):450-461. doi:10.2519/ jospt.2017.7255

• KEY WORDS: biomechanics, facet capsular ligament, nociception, sensitization, whiplash

whole.<sup>1,66,67,108</sup> The pathology associated with those tissue injuries includes microstructural damage to the collagen fibrous matrix of the capsular ligament, synovial fold pinching, and/or degenera-

tive changes to the articular cartilage, which can lead to osteoarthritis.67,80,85 Because the facet joints are innervated by mechanoreceptive and nociceptive afferent fibers,<sup>5,14,42</sup> any abnormal loading of the facet joint can also generate forces that mechanically load those afferents and initiate a host of pathophysiological responses that can lead to pain.43,53,54,57 In particular, injury of the innervated ligament tissue that encapsulates the synovial joint has the potential to generate pain (FIGURE 1).<sup>53,54</sup> As such, this commentary focuses on the physiological mechanisms by which biomechanical loading of the facet capsule can lead to pain, and the challenges in defining relevant thresholds for pain, biomechanical tissue injury, and neuronal responses, by integrating findings from basic science studies to inform the clinical management and/or diagnosis of whiplash-mediated facet pain.

When considering pain responses, it is always necessary to recognize that the sensory and emotional experiences of pain play a role in the clinical presentation.<sup>56</sup> Delineating and integrating each of these to understand whiplash pain

<sup>1</sup>Department of Bioengineering, University of Pennsylvania, Philadelphia, PA. <sup>2</sup>Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA. This work was funded by grants from the National Institutes of Health (U01EB016638) and the Catherine Sharpe Foundation. The authors certify that they have no affiliations with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the article. Address correspondence to Dr Beth A. Winkelstein, Department of Bioengineering, University of Pennsylvania, 210 South 33rd Street, 240 Skirkanich Hall, Philadelphia, PA 19104-6392. E-mail: winkelst@seas.upenn.edu 
Copyright ©2017 Journal of Orthopaedic & Sports Physical Therapy<sup>®</sup>



cord and transmit sensory information

from the periphery to the central ner-

such, the nociceptive signaling under-

conditions, can initiate peripheral sen-

responsiveness to a normally nonnox-

response to a normally subthreshold

stimulus.56 Sensitization can occur with-

in a nociceptive neuron's receptive field

in the periphery or to neurons communi-

Sensitization can manifest symptomati-

cally as hyperalgesia, which is increased pain from a normally noxious stimulus,

and/or allodynia, which is pain due to a

cal when they outlast the tissue injury vous system  $(CNS)^{4,8,14,41,42}$  (FIGURE 1). As and drive the persistence of pain.4 In humans, clinical assessment of both lying facet-mediated pain, under some evoked and spontaneous sensory (eg, sensitization) and emotional pain sympsitization and/or central sensitization.56 toms may be performed using a variety Sensitization is the increased neuronal of quantitative sensory testing methods<sup>20,31,99</sup> and also with patient questionnaires.91,93 These studies have identified ious stimulus and/or the presence of a the complex physical and psychological clinical presentation of whiplash and inferred relationships between the traumatic injuries sustained in whiplash and cating nociceptive signals in the CNS.56 the clinical symptoms that develop. However, clinical studies of the symptoms of facet-mediated pain and whiplash are limited in their ability to inform about the physiological mechanisms underly-

tral sensitization can become pathologi-

ing pain onset and/or maintenance. The same pain symptoms evaluated clinically have been shown to be detectable and robust in animal models,47,54 and are especially useful considering the wellestablished dermatomal mapping that has been defined across a number of species.53,97 As such, in vivo models provide useful platforms to integrate assays defining mechanics, physiology, and symptoms to define and understand painful injury and whiplash. Given the ability to study the physiological mechanisms of facet-mediated pain in vivo, the majority of studies throughout this commentary focus on findings in the rodent.

βIII-tubulin

substance P

200 µm

Baseline

Spinal cord

0

0

Dorsa horn

Noxious pinch

Although rodent models are useful in defining the pathophysiological mechanisms involved in the initiation and maintenance of facet-mediated pain, they are quite distinct from human models. An important distinction between species is their life span, which must be considered to understand the effects of timing between injury and symptom presentation in the human. Given

the typical life span of the rat, 13 days is equivalent to 1 human year.82 This relationship varies with developmental age in the rat. During adolescence it is approximately 10 days, during adulthood it is more like 12 days, and it is 17 days in the aged rat.82 In patients with whiplash, pain symptoms can develop within hours after injury.59,64,92 Although pain can resolve in some patients within 3 months, symptoms that last longer than 3 to 6 months are taken as chronic.<sup>3,64,77,83</sup> Given the relationship between the age of the rodent and that of the human, approximately 2.5 to 4.5 rodent-days correspond to 3 months in the human, and approximately 5 to 8.5 rodent-days correspond to 6 months in the human. This temporal scaling means that findings in the rodent that occur after 5 days of injury simulate the time when pain transitions from acute/subacute to chronic in the human. Further, pain in the rodent lasting more than 8.5 days has likely transitioned to the chronic stage. Although rodent models are valuable in providing controlled investigations into relationships between injury, pain, and molecular and chemical mechanisms throughout the various stages of the development of whiplash pain, none has investigated the longterm disability associated with whiplash.

To understand the physiological basis of facet-mediated pain in a clinical context, pain symptoms of individuals with whiplash are briefly reviewed, followed by a discussion of their manifestation after excessive facet stretch in the rat. In the next section, the macroscopic kinematics and microscopic tissue injury of facet tissues are discussed as they occur during whiplash and simulated painful whiplash injury. The effect of excessive mechanical injury on neuronal responses is then reviewed in the context of both in vivo and in vitro models. Finally, several challenges of integrating biomechanical and neuronal findings across scales and species are presented, with a focus on both translation of biomechanical and physiological injury thresholds and the difficulties introduced by the heterogeneities of the facet anatomy.

#### **Pain Symptoms**

In patients, pain symptoms present as early as a few hours after whiplash injury, and persistent pain has been reported for up to 2 years after exposure.59,64,92 Patients with whiplash injury exhibit both focal and widespread hypersensitivity during quantitative sensory tests, including decreased pain thresholds in response to mechanical and thermal stimuli.81,92,93 Those individuals who go on to develop persistent pain show signs of altered central pain processing, like diffuse mechanical hyperalgesia, thermal hyperalgesia, and/or lower thresholds to painful electrical stimulation, as early as 1 month after injury.<sup>21,31,92,93</sup> Patients with chronic pain exhibit primary mechanical hyperalgesia over the back of the cervical spine, in a "coat hanger" distribution indicative of peripheral nociceptor sensitization.<sup>21,81</sup> These patients are also hypersensitive to pressure, heat, and cold stimuli at sites distant from the cervical spine, including over the median, radial, and ulnar nerve trunks in the arm and over the tibialis anterior muscle.81 Together, these studies demonstrate that generalized and widespread secondary hypersensitivity is robust in individuals who sustain a whiplash-like exposure and indicative of central sensitization. Due to the large scope of that literature, it is not described in entirety here, but there are other sources in which this is reviewed extensively.<sup>20,31,99</sup>

In addition to the evoked measures of sensitization, whiplash-like exposures can induce spontaneous pain that is also suggestive of central sensitization. Patientreported sensory disturbances include spontaneous pain that is disproportionate to and/or occurs in the absence of any inciting event.<sup>7</sup> The inability to control such spontaneous pain is a primary motivator for individuals postwhiplash to seek medical care. The Neck Disability Index (NDI) is one of a variety of patient questionnaires used to quantify whiplash pain symptoms, including measures of selfperceived pain and disability associated with neck pain.<sup>101</sup> Poor and chronic clinical outcomes are associated with baseline NDI scores greater than 30/100.<sup>30,93</sup> More recently, NDI scores greater than 30/100 (or 15/50) have also been identified as a predictor and significant risk factor of poor patient outcomes.<sup>104</sup> In a study of patients with whiplash, those with a baseline NDI score of greater than 30 also showed signs of generalized hypersensitivity, suggesting a relationship between nonevoked spontaneous pain and central sensitization.<sup>92</sup> Because individuals postwhiplash present with symptoms of both evoked hypersensitivity and spontaneous pain, both of these aspects must be considered in animal studies.

Stretch injury of the facet capsular ligament comparable to that experienced during neck loading from a whiplash exposure induces symptoms in the rat that mimic clinical pain within 1 day following the joint injury and that persist for 3 to 4 weeks<sup>53,54</sup> (FIGURE 2A). A whiplash-like stretch injury to the facet joint induces sensitivity to mechanical stimuli over the back of the neck,53 in the same "coat-hanger" distribution observed clinically.21,81 In addition, more widespread sensitivity is also produced; mechanical hyperalgesia is observed with a decrease in paw withdrawal threshold to von Frey stimulation, lasting for 4 weeks (FIGURE 2A). Moreover, thermal hypersensitivity can be produced in the rat (FIGURE 2B). Although spontaneous pain cannot be self-reported in animals, several observational methods have been developed to assess it, including evaluating facial expressions and/or grooming behavior, analgesic self-administration, and autotomy.50,61 The Grimace Scale uses facial expression assessment to detect spontaneous pain across a variety of species, including in mice, 50,52,60 rats,15,24,65,68,87 and cats,35 and evaluates 4 different facial features that are rated on a severity scale of: 0 (not present), 1 (moderate), or 2 (present and severe) (FIGURE 2C).50 The Grimace Scale has been reported to detect spontaneous pain in rodent models of neuropathic pain.<sup>24,68</sup> Although the Grimace Scale has recently been shown to have the resolution to detect pain from injection of the inflammatory mediator



**FIGURE 2.** Different modalities of pain are detectable using various behavioral assays in rodent models of facet-mediated pain. (A) The withdrawal threshold of the forepaw is significantly reduced (\*P<.002) in response to stimulation with von Frey filaments after a facet capsule stretch simulating whiplash (painful; blue line) compared to physiologic nonpainful facet capsule stretch (orange line) (P<.008), with a lower threshold indicating increased mechanical hyperalgesia. (B) Forepaw sensitivity to thermal stimuli is also detectable following facet stimuli; the withdrawal latency to a heat source is lowered (\*P<.009) after an intra-articular facet injection of nerve growth factor (blue bar) but is not induced after ablation of the peptidergic afferents in the facet (orange bar) (P<.002), with a lower latency time indicating increased thermal hyperalgesia. (C) The grimace scores are immediately elevated (\*P<.007) in that same painful condition as in B; the published threshold for spontaneous pain (0.67) is shown by the dashed line.<sup>65</sup> The mean grimace score is the average of ratings for 4 action units: (1) orbital tightening, (2) whisker change, (3) nose/cheek flattening, and (4) ear change. Corresponding scores are shown in representative images, with none (0), moderate (1), and severe (2). \*Differences compared to a group's own baseline.

nerve growth factor into the facet joint (FIGURE 2C), it has yet to be investigated for use after a mechanical facet injury. Given the prevalence of spontaneous pain in individuals with whiplash,<sup>91,93</sup> developing robust and sensitive methods to evaluate spontaneous pain in animal models would provide translational value. Rodent studies have shown that varying the severity of the mechanical facet joint injury (ie, the magnitude of facet capsule stretch) directly affects the development and severity of pain symptoms.29,55 Supraphysiologic capsular stretch matching that of whiplashlike magnitudes is required to induce pain, but stretch at magnitudes comparable to those experienced during physiological joint loading does not induce pain.28,54 Although capsular stretch induces pain symptoms that are magnitude dependent,<sup>29,55</sup> pain is not further increased if the capsule undergoes failure.53,109 These behavioral studies demonstrate that an intact facet capsule is required for pain development, which supports the notion that afferent fiber signaling is requisite to transmit sensory information from the periphery to the CNS (FIGURE 1).47,86,109 Together, in vivo and clinical studies of facet injury have found that aspects and consequences of subfailure biomechanical loading to the intact facet capsule have critical contributions to pain development. As such, nociception may be driven by the transduction of the multiscale tissue and joint kinematics to physiological cascades of resident afferents.

#### Kinematics and Facet Tissue Injury During Whiplash

The macroscopic kinematics, or motions, of the cervical spine during whiplash ex-

posures have been extensively studied using both human in vivo and cadaveric in vitro methods and demonstrated that the spine undergoes a characteristic "Sdeformation."<sup>6,22,23,40,58,114</sup> During a motor vehicle collision, this abnormal deformation is induced approximately 60 to 100 milliseconds after vehicle impact due to the torso moving forward and upward prior to the movement of the head. It is only approximately 85 to 140 milliseconds after the initial vehicle impact that the head rotates backward, before both the head and torso rebound forward due to the support of the seat and headrest, and decelerate following the impact.6,23 Although the cervical spine has been shown to not undergo supraphysiological intervertebral rotation during such exposure, local tissue injury has been defined to result from abnormal kinematics

between vertebrae.<sup>6,67</sup> As such, whiplash exposures can increase the loading of the individual tissue structures in the spine, and particularly the facet joint. In addition to directly loading and damaging the facet capsule via tensile loading, cartilage and synovium deformations have also been reported.37,44,67,90 Mechanical facet capsule loading, in addition to having the potential to load nociceptive afferents embedded in it, also produces laxity under some conditions that produce pain.39,70 All of these local tissue-loading environments have the potential to result in joint instability, which can lead to other alterations in the kinematics of the overall joint and its capsular ligament during normal activities.41

Maximum principal strains quantify the greatest relative deformation in a tissue and are estimated using changes in the tissue configuration. Strain is a unitless metric that is often measured using imaging of materials while they are under load. Biomechanical thresholds for tissue loading have been established for pain in the cadaver and in animal systems by measuring strains across the facet capsule. In the rat, supraphysiologic (approximately 20%-30%) strains imposed during dynamic facet capsule stretch at a rate of 500%/s, which matches that sustained by humans,66,90,95,113 consistently induced pain, while those in the physiologic range (approximately 6%-15%) did not induce pain.<sup>19,26,27,29</sup> Of note, the strain magnitudes that induce pain in vivo are lower than the biomechanical strains at failure of the facet capsule, which have been reported at approximately 35% in posterior retraction<sup>84</sup> and approximately 65% in distraction,108 though large variability exists between subjects. This is not surprising given that complete transection of the capsule, simulating rupture, does not produce sustained pain in vivo.<sup>109</sup> Indeed, this is consistent with the lack of capsule ruptures in cadaveric studies of whiplash simulations.33,66,67,113 In this way, modeling specific scenarios of facet capsule stretch in vivo has provided complementary supportive evidence that

an intact capsule is required for pain generation, an assertion that was previously only hypothesized from cadaveric simulations.

Full strain-field measurements across the surface of the human cadaveric facet capsule and in vivo in the rat exhibit heterogeneity during both physiological flexion/ extension and joint retraction, simulating whiplash exposure (FIGURE 3A).72,74,84,108 Because strain magnitude has been shown to directly relate to the potential for and extent of pain, a heterogeneous strain field throughout an innervated capsule may also have variable potential for activating afferents, or at the least present heterogeneous afferent activation. Anatomical studies of the facet capsule evaluating the macroscopic and microscopic matrix composition and orientation of those components have shown that the facet capsule is composed of an outer layer of primarily collagen fibers orientated across the facet joint, while in its inner layer there are more randomly orientated elastic fibers.111,112 The thickness of the outer layer of the capsule, and the length of the collagen fibers within it, vary with the anatomic location of the capsule, as does the proportion of elastic fibers within the collagen matrix.<sup>111,112</sup> Because the microstructure of the capsular ligament dictates the biomechanical function and potential for injury, any variation in capsular microstructure likely corresponds to the functional ability of the capsule to guide and limit motions of the facet joint. The greater proportion of elastic fibers in the posteroinferior aspect corresponds to the large strains that are sustained in that region during extension and the potential for recovery to the neutral position with minimal risk of impingement.90,111-113 Considering this close interplay between the local tissue structure and the function of the facet capsular ligament, a model of how local damage may occur due to abnormal whiplash facet kinematics emerges. Furthermore, with altered local loading, as has been corroborated by the altered local strains, it is likely that capsule damage can still occur, despite strains remaining below the catastrophic failure threshold of 35% to 65%. However, the heterogeneous structure of the facet capsule also makes it challenging to determine local damage based on strain, because relationships between strain and damage are not necessarily correlative.

The complexity introduced by the heterogeneity of the facet capsule's kinematic response to load has led to work specifically assessing the local alterations in the ligament's microstructure. Quantitative polarized light imaging is an optical technique that exploits the natural birefringent optical property of collagen molecules to quantify the dynamic reorganization of collagen fibers during mechanical loading, and has been used extensively to evaluate soft tissue biomechanics and other collagenous tissue equivalents.49,76,79,98 Using this approach, collagen fiber realignment during tensile and posterior retraction loading of isolated human cadaveric facets, and tensile loading of isolated rat facets, has been defined.<sup>70,72,74-76</sup> In particular, those studies collectively demonstrate that areas with the highest fiber realignment correspond to those regions with microstructural damage to the collagen matrix (FIGURE 3B). These studies have shown that areas of greatest fiber realignment are significantly correlated with subsequent rupture,<sup>70,72,76</sup> but do not necessarily correspond to areas of peak maximum principal or shear strain.72,76 Together, these findings suggest that collagen realignment may be a more sensitive indicator of microstructural injury than strain measurements, and further highlight the possibility that afferent fibers may be more susceptible to activation if they reside in regions where the collagenous matrix undergoes abnormal deformation. Nevertheless, fiber realignment is correlated with areas in the ligament in which there is unrecovered strain after whiplash-like loading.<sup>74</sup> This spatial association supports the hypothesis that local changes in microstructural organization induced by loading known to be painful may contribute to the altered mechanical function of facet tissues. Fur-



the capsular surface strains during loading. The grid on the capsular surface is tracked by 2 cameras, which are used to estimate capsule deformation and 3-D strain fields during vertebral loading. (B) A fiber alignment map (shown in red lines), generated by polarized light imaging, shows collagen fiber alignment and its reorganization during facet loading, which alters the local biomechanical environment of any resident afferents in the ligament's collagen matrix. (C) Safranin O staining of the rat C6-7 facet, 6 weeks after facet joint distraction simulating physiological loading, shows the proteoglycan content of the facet joint cartilage (red); the close-up (inset) shows that facet cartilage does not exhibit signs of joint degeneration after nonpainful facet capsule loading.

ther, such deformation(s) of the matrix in a neuron's local environment may contribute to and/or drive nociceptive signaling from the joint.

To identify a single best predictor of microstructural damage in the facet capsular ligament remains difficult. Nevertheless, the studies highlighted here suggest that if laboratory research could focus on elucidating mechanisms of microscopic mechanosensation within the capsular ligament, then the broader basic science and clinical communities could better identify a biomechanical predictor for painful injury. Last, although the focus of this commentary has been on how the biomechanical environment can drive nociception, facet-mediated pain also can be induced by degenerative states.32,45,62 A host of biochemical cascades are initiated during joint degeneration that can induce degradation of facet tissues, including the articular cartilage and the capsular ligament (FIGURE 3C). Understanding the

relationships between degeneration, nociception, and the onset of pain would also inform the mechanisms underlying injury-induced facet pain, because degeneration-associated tissue degradation has the potential to result in the altered kinematics discussed here.

**Neuronal Responses to Excessive Stretch** Stretching the facet capsule beyond its physiologic limit can lead to altered physiology and morphology of the afferent neurons within the capsule, including changes in neuronal hyperexcitability and altered expression of neurotransmitters and other nociceptive molecules, both of which can contribute to pain (FIGURE 1). $^{12,17,27,41,43,55,57,71}$ Mechanical stretch of the facet to failure (mean  $\pm$  SD, 72.9%  $\pm$  7.1% strain) produces morphological abnormalities (ie, focal swelling, vacuolations, and terminal retraction balls) in the axons innervating the facet capsule in the goat.43 However, as described above, subfailure stretch of the facet capsule exceeding physiologic strains is sufficient to damage the ligament's microstructure and induce pain.<sup>27,76</sup> As such, characterizing the functional changes of neurons and understanding their relationships to the local injury mechanisms during loading below the tissue failure threshold are important, and many studies have initiated these investigations using both in vivo and in vitro models.

The primary afferents that innervate the facet joint and its capsular ligament respond to different thresholds for activation by mechanical stimuli.<sup>14,57</sup> Excessive strains that induce behavioral hypersensitivity also induce electrophysiological changes in neurons during and after capsular stretch.<sup>14,57</sup> For example, lowand high-threshold mechanoreceptors identified in the facet joint of the goat are activated by strains of 10% to 15% and 25% to 47%, respectively.<sup>14,57</sup> It has been shown that strains above 38%  $\pm$  12% induce afterdischarge in the neurons

after loading is removed.<sup>14,57</sup> Interestingly, these strain magnitudes are consistent with those associated with pain27,53 and are also comparable to those generated during whiplash-like neck loading and those inducing microscopic injury of the capsular ligament in biomechanical testing.66,76,84 Together, these findings suggest that the local mechanical environment of the afferent fibers in the facet capsule likely plays an important role in modulating their responses to excessive joint stretch. This notion is further supported by in vitro work using a neuron-collagen gel construct system that mimics the capsule structure and innervation. Imposing bulk strains greater than 11% to a gel increases phosphorylation of extracellularregulated kinase (ERK), an indicator of neuron activation, and causes collagen reorganization.115 This finding demonstrates that strains sufficiently large to initiate a neuronal response can also change the microstructure of the neuron's environment. These in vitro results suggest that the strain thresholds for neuronal activation (ERK phosphorylation) and local tissue injury (collagen matrix reorganization) may be the same.<sup>115</sup>

Journal of Orthopaedic & Sports Physical Therapy® Downloaded from www.jospt.org at University of Pennsylvania Library on August 26, 2017. For personal use only. No other uses without permission. Copyright © 2017 Journal of Orthopaedic & Sports Physical Therapy®. All rights reserved.

In addition to immediate neuronal responses, facet capsular loading that induces behavioral hypersensitivity in the rat is also associated with many sustained modifications in the nociceptive signaling from the primary afferents that are evident in the DRG. Protein expression of the nociceptive neurotransmitter, substance P, is increased in the DRG after painful facet joint stretch by day 7, and that change is absent in nonpainful stretch.55 Capsular stretch-induced increases in DRG expression of the metabotropic glutamate receptor 5 (mGluR5) and its second messenger, protein kinase C-epsilon (PKCE), are strain dependent and are not evident until 7 days after the initial injury.<sup>27,105</sup> The late upregulation of these molecules suggests that they may play a role in the later nociceptive pathways involved in injury-induced pain. Furthermore, because dorsal horn hyperexcitability and increased spontaneous activity develop between 6 and 24 hours after facet injury,<sup>18</sup> it is unlikely that these neuromodulators play a role in the initial electrophysiology responses of afferents that parallel the onset of hypersensitivity. Because these neuromodulators (substance P, mGluR5, and PKCE) are involved in neuroplasticity and pain,<sup>13,100,103</sup> their delayed elevation implies that the afferents undergo persistent activation and/or dysfunction after painful loading has occurred. Because axonal degeneration is known to take 7 days to develop,<sup>36,78</sup> it may contribute to the late onset of modified nociceptive signaling.

A complex dysregulation of glutamatergic signaling in the spinal cord accompanies excessive facet stretch and drives nociception that causes pain. Painful facet injury modifies the spinal expression of a number of nociceptive molecules involved in excitatory glutamatergic signaling, including phosphorylated ERK, mGluR5, PKCE, and ionotropic glutamate receptor N-methyl-D-aspartate subunit.17,27,105 Expression of each of these nociceptive molecules is increased in the spinal cord along the same time course as sustained pain symptoms and spinal hyperexcitability.<sup>17,27,105</sup> In addition to increases in expression of glutamate receptors, expression of glutamate transporters on astrocytes and neurons, which regulate the clearance of glutamate away from synapses, like glutamate aspartate transporter, glutamate transporter 1, and excitatory amino-acid carrier 1, is also altered in the spinal cord 1 week after painful facet stretch. While the astroctyic glutamate transporter (glutamate aspartate transporter) is upregulated 1 week after painful injury, both glutamate transporter 1 and excitatory amino-acid carrier 1, which are expressed on other cells, are downregulated, pointing to the widespread and complicated dysregulation of glutamate in pain from facet joint injury.<sup>17,27,29</sup>

Nociceptors innervating the facet joint transmit noxious stimuli from peripheral terminals to the spinal cord via action potential propagation. That peripheral inputs lead to increased neuronal firing is evidence of central sensitization (FIGURE 1).4 Increases in spontaneous and evoked neuronal firing in the spinal cord parallel the behavioral hypersensitivity that develops between 6 and 24 hours after excessive subfailure facet joint stretch in rats.18 A functional role of early afferent activity in pain transmission has been corroborated by a study in the rat that blocked afferent activity with a single joint injection of the anesthetic bupivacaine at early times after injury. Bupivacaine attenuated pain symptoms and prevented the development of spinal neuronal hypersensitivity when given immediately after injury, while the same administration at times even as early as 4 days later had no effect on modifying either response compared to the typical injury response.17 This narrow and early establishment of spinal modifications strongly supports a similarly narrow temporal window for intervention after a whiplash injury during which the onset of spinal mechanisms of sensitization can be prevented. The initial injury-induced hyperexcitability of dorsal horn neurons that develops by 24 hours after injury persists for at least 7 days in the rat.<sup>17,19,71</sup>

The sustained hyperexcitability of spinal neurons has been speculated to be maintained by structural and/or functional plasticity in the spinal cord.<sup>4,51</sup> Indeed, structural plasticity is evident in the superficial dorsal horn, with approximately a 50% increase in the number of excitatory synapses that are present in the spinal cord, accompanied by a decrease in inhibitory synapses.<sup>19,38</sup> This synaptic plasticity can potentiate the excitatory signaling that manifests as hyperalgesia and allodynia. These changes in synapse numbers are accompanied by both increases in the number of spinal cord neurons classified as nociceptive and decreases in the number of neurons classified as low-threshold mechanoreceptors.<sup>19,71</sup> Clinically, these same phenotypic shifts can manifest as decreased pain thresholds to various stimuli.4 It is important to note that this phenotypic switch is only observed when

the strain across the facet capsule exceeds physiological strains and produces pain,<sup>71</sup> further supporting the notion that plastic changes in the spinal cord may also be severity dependent. Indeed, the decrease in inhibitory synapses observed 14 days after painful injury is also correlated with the severity of facet injury.<sup>38</sup> Collectively, these studies provide evidence of spinal cord plasticity following painful facet injury that is severity dependent and can potentiate nociception of facet-mediated pain.

Facet joint trauma is a complex injury involving both mechanical insults as well as inflammatory cascades that stimulate neurons. A review of the cascades involved in inflammatory pain is beyond the scope of this commentary but can be found elsewhere.4,107 We do provide a brief review here of relevant findings following facet trauma as they may relate to whiplash. Like other chronic pain conditions, spinal astrocytes are activated for at least 14 days after painful facet stretch.16,17 Mechanical injury to the facet capsule also regulates the production of inflammatory mediators, including proinflammatory cytokines and neurotrophins, in the facet joint itself, as well as in the DRG.<sup>46,48,53,69</sup> Because peripheral inflammation increases hyperexcitability and substance P in DRG neurons, along with pain production,<sup>96,110</sup> recent studies have begun to elucidate the molecular mechanisms by which peripheral inflammation contributes to central sensitization in the context of facet-mediated pain. Recently, neurotrophins have been implicated both locally in the facet and to be more widespread in the CNS. Nerve growth factor (NGF) increases in the facet joint tissues as early as 1 day after a facet joint distraction that produces pain at that same time.46 Further, inhibiting NGF signaling also prevents the onset of pain and associated spinal neuron hyperexcitability when anti-NGF is given intra-articularly immediately after capsule stretch and before pain develops,46 suggesting a critical role of local NGF in initiating pain. Unlike NGF, expression of the neurotrophin brain-derived

neurotrophic factor (BDNF) increases in both the DRG and spinal cord at a later time (day 7), with intrathecal administration of the BDNF-sequestering molecule trkB-Fc after facet injury partially reducing pain.<sup>48</sup> Collectively, these NGF and BDNF studies not only reveal important novel pathways emerging as having critical roles in pain from whiplash injury, but also provide potential therapeutic targets for treating joint pain.

### The Challenges of Translating Basic Science to the Clinical Setting

Although in vivo and in vitro models continue to inform about the pathophysiology of nociception in facet-mediated pain, there are several challenges in translating that work to the human condition and understanding injury risk, as well as in guiding clinical treatment. Among the major challenges of understanding the biomechanical mechanisms of whiplash pain is related to defining thresholds for joint injury, neuronal activation and dysfunction, and pain. Although basic science studies collectively have defined thresholds for neuronal activation and the induction of pain, those studies are based on work in vivo in the rat and/or goat, or even in artificial constructs simulating the ligament.<sup>14,19,26,27,57,115</sup> Nonetheless, because a common, nondimensional biomechanical metric (strain) has been used across all of those studies, the findings are agnostic of species and/or scale, and it may therefore be possible to extend such findings to the human. The bigger challenges of understanding injury risk and predicting injury in humans are complicated by very complex and integrated systems at play in pain. For example, pre-existing physiological priming in the human could lower the threshold for neuronal activation and other responses. In fact, this has been shown in a rat model in which the typically physiologic facet loading is capable of producing pain if there is a prior exposure to chemical stimuli or prior loading.<sup>19,89</sup>

Although biomechanical metrics like strain can be used to compare cadaveric,

clinical, and animal studies that investigate mechanisms of whiplash, they do not fully capture the highly complicated anatomical and structural environment relevant to pain and injury. The highly variable structure of the facet capsular ligament, including its varied thickness, the variable length of the collagen fibers that comprise it, and the proportion of elastin fibers,<sup>111,112</sup> contributes to the heterogeneity of the facet capsule's biomechanical response to loading. As such, the above metrics fail to fully capture relevant mechanical response that may be highly influential in driving the physiological response. The microstructural reorganization of the facet capsule's extracellular matrix, composed mainly of collagen, is also heterogeneous, with more extensive collagen fibers in the posterior region of the capsule than in its lateral region.73 This regional variation in microstructure makes using any single injury metric as the gold standard challenging at best and inappropriate or inadequate at worst. Measurements of microstructural reorganization like collagen fiber realignment appear to be a better predictor of the onset of microstructural damage than strain measurements,72,76 which makes them a promising injury metric. However, acquiring such measurements remains technically difficult. Collagen fiber realignment, for example, is difficult to measure noninvasively or outside the laboratory, making it challenging to implement in studies of either global tissue responses or pain (in humans and/or animal models). Higherresolution strain-field measurements combined with analyses that quantify unrecovered strain could provide promising approaches to identify the local biomechanics that initiate mechanosensation in afferents. Furthermore, although kinematics of the cervical spine and the facet joint under whiplash-like loading are well defined, those complex kinematics are difficult to apply in either an animal model or in isolated tissue tests, and the heterogeneity of the tissue could result in kinematics that may not reflect the clinical scenario. This challenge is exacerbated

not only by the anatomical heterogeneity of the facet joint, but also by the scaling of biomechanical injury metrics to the in vivo environment.

While there is tremendous utility in relating thresholds for generating pathophysiological responses to the initiation of the cascades that regulate persistent pain, utilizing the emerging cellular and molecular schema for whiplash pain production has the greatest potential for informing and shaping clinical treatments. Indeed, work in animal models highlights potential points of modulation via altering or preventing aberrant neuronal activity,17,18,25 inflammatory cascades,26,28 and/or nociceptive signaling cascades.<sup>47,48,106</sup> Despite the effectiveness of such treatments in animal models, their translation to humans is challenging for many reasons. First, clinically, humans present with whiplash at varied times after the initial injury, and may or may not exhibit confounding predispositions and/or physiological states. As such, many of the treatments that are effective in vivo in basic science have effects only when administered in specific time frames after injury.<sup>17,28,47</sup> Because the clinical time between injury, treatment, and/ or an intervention is not uniform, presentation of pain symptoms after whiplashlike injuries is highly variable, creating an inherent disconnect between preclinical findings and those at the clinic. In addition, the human condition of whiplash is accompanied by many psychosocial factors that are not present in animal models, including catastrophizing,<sup>10,94</sup> fear avoidance,9 and confounding factors due to litigation,<sup>88</sup> among other forms of psychosocial stress.2,11,77,93 Although animal models are limited by not including these psychosocial factors, they also provide great utility in that physiological questions can be investigated without these confounding variables.

It is important also to recognize that there is a similar but equally important disconnect when moving from clinical studies to the laboratory. The pain systems that are most commonly assayed and reported for patients with whiplash are not easily translated to animal models. Certainly, spontaneous pain is commonly reported in patients with whiplash,91,93 and capturing the emotional components of pain is of the utmost importance in this syndrome. However, a reliable assessment of spontaneous pain in vivo in the laboratory remains the holy grail. Ultimately, establishing reliable assays and translatable studies, from both the laboratory and clinical realms, will help bridge activities elucidating molecular pathways of nociception and those in which treatment approaches are being trialed on patients with facet-mediated whiplash pain.

#### SUMMARY

ESPITE THE CHALLENGES OF MEANingfully integrating the basic science mechanisms of pain from joint trauma with clinical management and diagnosis, the interdisciplinary efforts crossing silos of clinical, engineering, and physiological research have gone a long way to developing a model schema for understanding whiplash-related pain. In this commentary, we reviewed aspects of the complex anatomical, biomechanical, and physiological consequences of whiplash loading to the facet joint. In particular, basic science studies using facet loading were related to work with humans, either in the clinic or in the laboratory. Owing to the complexity of this problem, we focused on the macroscopic work defining tissue injury at the organ scale, with complementary work at the microscale, to understand the responses of collagen and neuronal cells. Managing the pathology of facet pain requires an even deeper understanding of the anatomical tissues, neuronal innervation and response in the facet joint, the susceptibility of that joint and its constituents to varying magnitudes of biomechanical loading, and the temporal physiological responses of mechanosensation. Most important, perhaps, is that each and every one of these signals and responses

must be defined in the context of clinical pain symptoms. It is clear from the basic laboratory studies that the heterogeneous nature of the facet joint itself, and its cellular responses to painful loading, are primary contributors to the breadth of individual responses that are observed in patients with whiplash-related pain. Nevertheless, while a clear and consistent cellular/molecular schema for traumainduced facet pain is emerging (**FIGURE 1**), fully understanding the nature of facetmediated pain remains challenging. (**•**)

ACKNOWLEDGMENTS: The authors gratefully acknowledge Jeffrey V. Kras, Blythe Philips, Christine L. Weisshaar, Nicolas V. Jaumard, and Kyle P. Quinn for their contributions to data included in the figures.

#### REFERENCES

- Anderst WJ, Donaldson WF, 3rd, Lee JY, Kang JD. In vivo cervical facet joint capsule deformation during flexion-extension. Spine (Phila Pa 1976). 2014;39:E514-E520. https://doi.org/10.1097/ BRS.00000000000235
- Ariëns GA, van Mechelen W, Bongers PM, Bouter LM, van der Wal G. Psychosocial risk factors for neck pain: a systematic review. Am J Ind Med. 2001;39:180-193.
- Bannister G, Amirfeyz R, Kelley S, Gargan M. Whiplash injury. J Bone Joint Surg Br. 2009;91:845-850. https://doi. org/10.1302/0301-620X.91B7.22639
- Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell. 2009;139:267-284. https://doi.org/10.1016/j. cell.2009.09.028
- Bogduk N, Marsland A. The cervical zygapophysial joints as a source of neck pain. Spine (Phila Pa 1976). 1988;13:610-617.
- Bogduk N, Yoganandan N. Biomechanics of the cervical spine part 3: minor injuries. *Clin Biomech (Bristol, Avon)*. 2001;16:267-275. https:// doi.org/10.1016/S0268-0033(01)00003-1
- Borchers AT, Gershwin ME. Complex regional pain syndrome: a comprehensive and critical review. *Autoimmun Rev.* 2014;13:242-265. https://doi. org/10.1016/j.autrev.2013.10.006
- Braz JM, Nassar MA, Wood JN, Basbaum AI. Parallel "pain" pathways arise from subpopulations of primary afferent nociceptor. *Neuron*. 2005;47:787-793. https://doi.org/10.1016/j. neuron.2005.08.015
- Buitenhuis J, de Jong PJ. Fear avoidance and illness beliefs in post-traumatic neck pain. Spine (Phila Pa 1976). 2011;36:S238-S243. https://doi.

org/10.1097/BRS.0b013e3182388400

- Carriere JS, Thibault P, Milioto M, Sullivan MJ. Expectancies mediate the relations among pain catastrophizing, fear of movement, and return to work outcomes after whiplash injury. J Pain. 2015;16:1280-1287. https://doi.org/10.1016/j. jpain.2015.09.001
- Carroll LJ. Beliefs and expectations for recovery, coping, and depression in whiplash-associated disorders: lessening the transition to chronicity. Spine (Phila Pa 1976). 2011;36:S250-S256. https://doi.org/10.1097/BRS.0b013e31823881a4
- Cavanaugh JM, Lu Y, Chen C, Kallakuri S. Pain generation in lumbar and cervical facet joints. J Bone Joint Surg Am. 2006;88 suppl 2:63-67.
- Chang YW, Winkelstein BA. Schwann cell proliferation and macrophage infiltration are evident at day 14 after painful cervical nerve root compression in the rat. J Neurotrauma. 2011;28:2429-2438. https://doi.org/10.1089/neu.2011.1918
- Chen C, Lu Y, Kallakuri S, Patwardhan A, Cavanaugh JM. Distribution of A-delta and C-fiber receptors in the cervical facet joint capsule and their response to stretch. *J Bone Joint Surg Am*. 2006;88:1807-1816.
- 15. Chi H, Kawano T, Tamura T, et al. Postoperative pain impairs subsequent performance on a spatial memory task via effects on *N*-methyl-D-aspartate receptor in aged rats. *Life Sci*. 2013;93:986-993. https://doi.org/10.1016/j. lfs.2013.10.028
- Claycomb KI, Johnson KM, Winokur PN, Sacino AV, Crocker SJ. Astrocyte regulation of CNS inflammation and remyelination. *Brain Sci.* 2013;3:1109-1127. https://doi.org/10.3390/ brainsci3031109
- 17. Crosby ND, Gilliland TM, Winkelstein BA. Early afferent activity from the facet joint after painful trauma to its capsule potentiates neuronal excitability and glutamate signaling in the spinal cord. *Pain*. 2014;155:1878-1887. https://doi. org/10.1016/j.pain.2014.06.019
- Crosby ND, Weisshaar CL, Winkelstein BA. Spinal neuronal plasticity is evident within 1 day after a painful cervical facet joint injury. *Neurosci Lett*. 2013;542:102-106. https://doi.org/10.1016/j. neulet.2013.03.019
- Crosby ND, Zaucke F, Kras JV, Dong L, Luo ZD, Winkelstein BA. Thrombospondin-4 and excitatory synaptogenesis promote spinal sensitization after painful mechanical joint injury. *Exp Neurol*. 2015;264:111-120. https://doi.org/10.1016/j. expneurol.2014.11.015
- 20. Curatolo M, Müller M, Ashraf A, et al. Pain hypersensitivity and spinal nociceptive hypersensitivity in chronic pain: prevalence and associated factors. *Pain*. 2015;156:2373-2382. https://doi. org/10.1097/j.pain.00000000000289
- Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Giani C, Zbinden AM, Radanov BP. Central hypersensitivity in chronic pain after whiplash injury. *Clin J Pain*. 2001;17:306-315.
- **22.** Cusick JF, Pintar FA, Yoganandan N. Whiplash syndrome: kinematic factors influencing pain

#### patterns. Spine (Phila Pa 1976). 2001;26:1252-1258.

- 23. Dehner C, Elbel M, Schick S, Walz F, Hell W, Kramer M. Risk of injury of the cervical spine in sled tests in female volunteers. *Clin Biomech* (*Bristol, Avon*). 2007;22:615-622. https://doi. org/10.1016/j.clinbiomech.2007.02.004
- 24. De Rantere D, Schuster CJ, Reimer JN, Pang DS. The relationship between the Rat Grimace Scale and mechanical hypersensitivity testing in three experimental pain models. *Eur J Pain*. 2016;20:417-426. https://doi.org/10.1002/ejp.742
- 25. Dong L, Crosby ND, Winkelstein BA. Gabapentin alleviates facet-mediated pain in the rat through reduced neuronal hyperexcitability and astrocytic activation in the spinal cord. J Pain. 2013;14:1564-1572. https://doi.org/10.1016/j. jpain.2013.07.016
- 26. Dong L, Guarino BB, Jordan-Sciutto KL, Winkelstein BA. Activating transcription factor 4, a mediator of the integrated stress response, is increased in the dorsal root ganglia following painful facet joint distraction. *Neuroscience*. 2011;193:377-386. https://doi.org/10.1016/j. neuroscience.2011.07.059
- 27. Dong L, Quindlen JC, Lipschutz DE, Winkelstein BA. Whiplash-like facet joint loading initiates glutamatergic responses in the DRG and spinal cord associated with behavioral hypersensitivity. *Brain Res.* 2012;1461:51-63. https://doi.org/10.1016/j. brainres.2012.04.026
- Dong L, Smith JR, Winkelstein BA. Ketorolac reduces spinal astrocytic activation and PAR1 expression associated with attenuation of pain after facet joint injury. J Neurotrauma. 2013;30:818-825. https://doi.org/10.1089/neu.2012.2600
- 29. Dong L, Winkelstein BA. Simulated whiplash modulates expression of the glutamatergic system in the spinal cord suggesting spinal plasticity is associated with painful dynamic cervical facet loading. J Neurotrauma. 2010;27:163-174. https:// doi.org/10.1089/neu.2009.0999
- 30. Elliott JM, Courtney DM, Rademaker A, Pinto D, Sterling MM, Parrish TB. The rapid and progressive degeneration of the cervical multifidus in whiplash: an MRI study of fatty infiltration. Spine (Phila Pa 1976). 2015;40:E694-E700. https://doi. org/10.1097/BRS.00000000000891
- Elliott JM, Noteboom JT, Flynn TW, Sterling M. Characterization of acute and chronic whiplashassociated disorders. J Orthop Sports Phys Ther. 2009;39:312-323. https://doi.org/10.2519/ jospt.2009.2826
- 32. Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: the facet joints. Nat Rev Rheumatol. 2013;9:216-224. https://doi.org/10.1038/ nrrheum.2012.199
- 33. Grauer JN, Panjabi MM, Cholewicki J, Nibu K, Dvorak J. Whiplash produces an S-shaped curvature of the neck with hyperextension at lower levels. Spine (Phila Pa 1976). 1997;22:2489-2494.
- **34.** Hogg-Johnson S, van der Velde G, Carroll LJ, et al. The burden and determinants of neck pain in the general population: results of the Bone and Joint Decade 2000-2010 Task Force on

Neck Pain and Its Associated Disorders. *Spine* (*Phila Pa 1976*). 2008;33:S39-S51. https://doi. org/10.1097/BRS.0b013e31816454c8

- 35. Holden E, Calvo G, Collins M, et al. Evaluation of facial expression in acute pain in cats. J Small Anim Pract. 2014;55:615-621. https://doi. org/10.1111/jsap.12283
- **36.** Hubbard RD, Quinn KP, Martínez JJ, Winkelstein BA. The role of graded nerve root compression on axonal damage, neuropeptide changes, and pain-related behaviors. *Stapp Car Crash J.* 2008;52:33-58.
- 37. Inami S, Shiga T, Tsujino A, Yabuki T, Okado N, Ochiai N. Immunohistochemical demonstration of nerve fibers in the synovial fold of the human cervical facet joint. J Orthop Res. 2001;19:593-596. https://doi.org/10.1016/ S0736-0266(00)00048-6
- 38. Ita ME, Crosby ND, Bulka BA, Winkelstein BA. Painful cervical facet joint injury is accompanied by changes in the number of excitatory and inhibitory synapses in the superficial dorsal horn that differentially relate to local tissue injury severity. Spine (Phila Pa 1976). In press. https:// doi.org/10.1097/BRS.00000000001934
- **39.** Ivancic PC, Ito S, Torninaga Y, et al. Whiplash causes increased laxity of cervical capsular ligament. *Clin Biomech (Bristol, Avon)*. 2008;23:159-165. https://doi.org/10.1016/j. clinbiomech.2007.09.003
- 40. Ivancic PC, Panjabi MM, Ito S. Cervical spine loads and intervertebral motions during whiplash. *Traffic Inj Prev.* 2006;7:389-399. https://doi. org/10.1080/15389580600789127
- Jaumard NV, Welch WC, Winkelstein BA. Spinal facet joint biomechanics and mechanotransduction in normal, injury and degenerative conditions. J Biomech Eng. 2011;133:071010. https:// doi.org/10.1115/1.4004493
- Kallakuri S, Singh A, Chen C, Cavanaugh JM. Demonstration of substance P, calcitonin gene-related peptide, and protein gene product 9.5 containing nerve fibers in human cervical facet joint capsules. *Spine (Phila Pa 1976)*. 2004;29:1182-1186.
- 43. Kallakuri S, Singh A, Lu Y, Chen C, Patwardhan A, Cavanaugh JM. Tensile stretching of cervical facet joint capsule and related axonal changes. *Eur Spine J.* 2008;17:556-563. https://doi.org/10.1007/s00586-007-0562-0
- 44. Kaneoka K, Ono K, Inami S, Hayashi K. Motion analysis of cervical vertebrae during whiplash loading. Spine (*Phila Pa* 1976). 1999;24:763-769; discussion 770.
- 45. Kim JS, Ali MH, Wydra F, et al. Characterization of degenerative human facet joints and facet joint capsular tissues. Osteoarthritis Cartilage. 2015;23:2242-2251. https://doi.org/10.1016/j. joca.2015.06.009
- 46. Kras JV, Kartha S, Winkelstein BA. Intra-articular nerve growth factor regulates development, but not maintenance, of injury-induced facet joint pain & spinal neuronal hypersensitivity. Osteoarthritis Cartilage. 2015;23:1999-2008. https://doi.

org/10.1016/j.joca.2015.06.012

- 47. Kras JV, Weisshaar CL, Pall PS, Winkelstein BA. Pain from intra-articular NGF or joint injury in the rat requires contributions from peptidergic joint afferents. *Neurosci Lett.* 2015;604:193-198. https://doi.org/10.1016/j.neulet.2015.07.043
- 48. Kras JV, Weisshaar CL, Quindlen J, Winkelstein BA. Brain-derived neurotrophic factor is upregulated in the cervical dorsal root ganglia and spinal cord and contributes to the maintenance of pain from facet joint injury in the rat. J Neurosci Res. 2013;91:1312-1321. https://doi.org/10.1002/ jnr.23254
- 49. Lake SP, Hald ES, Barocas VH. Collagen-agarose co-gels as a model for collagen-matrix interaction in soft tissues subjected to indentation. J *Biomed Mater Res A*. 2011;99:507-515. https:// doi.org/10.1002/jbm.a.33183
- Langford DJ, Bailey AL, Chanda ML, et al. Coding of facial expressions of pain in the laboratory mouse. Nat Methods. 2010;7:447-449. https:// doi.org/10.1038/nmeth.1455
- Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10:895-926. https:// doi.org/10.1016/j.jpain.2009.06.012
- 52. Leach MC, Klaus K, Miller AL, Scotto di Perrotolo M, Sotocinal SG, Flecknell PA. The assessment of post-vasectomy pain in mice using behaviour and the Mouse Grimace Scale. *PLoS One*. 2012;7:e35656. https://doi.org/10.1371/journal. pone.0035656
- 53. Lee KE, Davis MB, Winkelstein BA. Capsular ligament involvement in the development of mechanical hyperalgesia after facet joint loading: behavioral and inflammatory outcomes in a rodent model of pain. J Neurotrauma. 2008;25:1383-1393. https://doi.org/10.1089/ neu.2008.0700
- 54. Lee KE, Thinnes JH, Gokhin DS, Winkelstein BA. A novel rodent neck pain model of facetmediated behavioral hypersensitivity: implications for persistent pain and whiplash injury. J Neurosci Methods. 2004;137:151-159. https://doi. org/10.1016/j.jneumeth.2004.02.021
- 55. Lee KE, Winkelstein BA. Joint distraction magnitude is associated with different behavioral outcomes and substance P levels for cervical facet joint loading in the rat. J Pain. 2009;10:436-445. https://doi.org/10.1016/j.jpain.2008.11.009
- Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. Pain. 2008;137:473-477. https://doi.org/10.1016/j.pain.2008.04.025
- 57. Lu Y, Chen C, Kallakuri S, Patwardhan A, Cavanaugh JM. Neural response of cervical facet joint capsule to stretch: a study of whiplash pain mechanism. *Stapp Car Crash J.* 2005;49:49-65.
- 58. Luan F, Yang KH, Deng B, Begeman PC, Tashman S, King Al. Qualitative analysis of neck kinematics during low-speed rear-end impact. *Clin Biomech (Bristol, Avon)*. 2000;15:649-657. https://doi.org/10.1016/S0268-0033(00)00031-0
- **59.** Manchikanti L, Boswell MV, Singh V, Pampati V, Damron KS, Beyer CD. Prevalence of facet

joint pain in chronic spinal pain of cervical, thoracic, and lumbar regions. *BMC Musculoskelet Disord*. 2004;5:15. https://doi. org/10.1186/1471-2474-5-15

- 60. Matsumiya LC, Sorge RE, Sotocinal SG, et al. Using the Mouse Grimace Scale to reevaluate the efficacy of postoperative analgesics in laboratory mice. J Am Assoc Lab Anim Sci. 2012;51:42-49.
- Mogil JS. Animal models of pain: progress and challenges. Nat Rev Neurosci. 2009;10:283-294. https://doi.org/10.1038/nrn2606
- Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage. 2013;21:1145-1153. https://doi.org/10.1016/j. joca.2013.03.018
- 63. Nolet PS, Côté P, Kristman VL, Rezai M, Carroll LJ, Cassidy JD. Is neck pain associated with worse health-related quality of life 6 months later? A population-based cohort study. Spine J. 2015;15:675-684. https://doi.org/10.1016/j. spinee.2014.12.009
- **64.** Norris SH, Watt I. The prognosis of neck injuries resulting from rear-end vehicle collisions. *J Bone Joint Surg Br.* 1983;65:608-611.
- 65. Oliver V, De Rantere D, Ritchie R, Chisholm J, Hecker KG, Pang DS. Psychometric assessment of the Rat Grimace Scale and development of an analgesic intervention score. *PLoS One*. 2014;9:e97882. https://doi.org/10.1371/journal. pone.0097882
- 66. Panjabi MM, Cholewicki J, Nibu K, Grauer J, Vahldiek M. Capsular ligament stretches during in vitro whiplash simulations. J Spinal Disord. 1998;11:227-232.
- Pearson AM, Ivancic PC, Ito S, Panjabi MM. Facet joint kinematics and injury mechanisms during simulated whiplash. *Spine (Phila Pa 1976)*. 2004;29:390-397.
- **68.** Philips BH, Weisshaar CL, Winkelstein BA. Use of the rat grimace scale to evaluate neuropathic pain in a model of cervical radiculopathy. *Comp Med.* 2017;67:34-42.
- 69. Pinski SE, King KB, Davidson BS, Zhou BH, Lu Y, Solomonow M. High-frequency loading of lumbar ligaments increases proinflammatory cytokines expression in a feline model of repetitive musculoskeletal disorder. Spine J. 2010;10:1078-1085. https://doi.org/10.1016/j.spinee.2010.08.030
- 70. Quinn KP, Bauman JA, Crosby ND, Winkelstein BA. Anomalous fiber realignment during tensile loading of the rat facet capsular ligament identifies mechanically induced damage and physiological dysfunction. *J Biomech*. 2010;43:1870-1875. https://doi.org/10.1016/j. jbiomech.2010.03.032
- Quinn KP, Dong L, Golder FJ, Winkelstein BA. Neuronal hyperexcitability in the dorsal horn after painful facet joint injury. *Pain*. 2010;151:414-421. https://doi.org/10.1016/j.pain.2010.07.034
- 72. Quinn KP, Winkelstein BA. Altered collagen fiber kinematics define the onset of localized ligament damage during loading. J Appl Physiol (1985). 2008;105:1881-1888. https://doi.org/10.1152/ japplphysiol.90792.2008

- 73. Quinn KP, Winkelstein BA. Cervical facet capsular ligament yield defines the threshold for injury and persistent joint-mediated neck pain. *J Biomech.* 2007;40:2299-2306. https://doi. org/10.1016/j.jbiomech.2006.10.015
- 74. Quinn KP, Winkelstein BA. Detection of altered collagen fiber alignment in the cervical facet capsule after whiplash-like joint retraction. Ann Biomed Eng. 2011;39:2163-2173. https://doi. org/10.1007/s10439-011-0316-3
- 75. Quinn KP, Winkelstein BA. Full field strain measurements of collagenous tissue by tracking fiber alignment through vector correlation. *J Biomech*. 2010;43:2637-2640. https://doi.org/10.1016/j. jbiomech.2010.05.008
- 76. Quinn KP, Winkelstein BA. Vector correlation technique for pixel-wise detection of collagen fiber realignment during injurious tensile loading. J Biomed Opt. 2009;14:054010. https://doi. org/10.1117/1.3227037
- 77. Radanov BP, Sturzenegger M, Di Stefano G. Longterm outcome after whiplash injury. A 2-year follow-up considering features of injury mechanism and somatic, radiologic, and psychosocial findings. *Medicine (Baltimore)*. 1995;74:281-297.
- 78. Ramer MS, French GD, Bisby MA. Wallerian degeneration is required for both neuropathic pain and sympathetic sprouting into the DRG. *Pain*. 1997;72:71-78. https://doi.org/10.1016/ S0304-3959(97)00019-5
- 79. Sander EA, Stylianopoulos T, Tranquillo RT, Barocas VH. Image-based biomechanics of collagenbased tissue equivalents. *IEEE Eng Med Biol Mag.* 2009;28:10-18. https://doi.org/10.1109/ MEMB.2009.932486
- **80.** Schofferman J, Bogduk N, Slosar P. Chronic whiplash and whiplash-associated disorders: an evidence-based approach. J Am Acad Orthop Surg. 2007;15:596-606.
- Scott D, Jull G, Sterling M. Widespread sensory hypersensitivity is a feature of chronic whiplashassociated disorder but not chronic idiopathic neck pain. *Clin J Pain*. 2005;21:175-181.
- **82.** Sengupta P. The laboratory rat: relating its age with human's. *Int J Prev Med*. 2013;4:624-630.
- Seroussi R, Singh V, Fry A. Chronic whiplash pain. *Phys Med Rehabil Clin N Am*. 2015;26:359-373. https://doi.org/10.1016/j.pmr.2015.01.003
- 84. Siegmund GP, Myers BS, Davis MB, Bohnet HF, Winkelstein BA. Mechanical evidence of cervical facet capsule injury during whiplash: a cadaveric study using combined shear, compression, and extension loading. *Spine (Phila Pa 1976)*. 2001;26:2095-2101.
- 85. Siegmund GP, Winkelstein BA, Ivancic PC, Svensson MY, Vasavada A. The anatomy and biomechanics of acute and chronic whiplash injury. *Traffic Inj Prev*. 2009;10:101-112. https:// doi.org/10.1080/15389580802593269
- 86. Smith AD, Jull G, Schneider GM, Frizzell B, Hooper RA, Sterling M. Modulation of cervical facet joint nociception and pain attenuates physical and psychological features of chronic whiplash: a prospective study. PM R. 2015;7:913-921. https://

doi.org/10.1016/j.pmrj.2015.03.014

- 87. Sotocinal SG, Sorge RE, Zaloum A, et al. The Rat Grimace Scale: a partially automated method for quantifying pain in the laboratory rat via facial expressions. *Mol Pain*. 2011;7:55. https://doi. org/10.1186/1744-8069-7-55
- Spearing NM, Connelly LB, Gargett S, Sterling M. Does injury compensation lead to worse health after whiplash? A systematic review. *Pain*. 2012;153:1274-1282. https://doi.org/10.1016/j. pain.2012.03.007
- 89. Sperry MM, Ita ME, Kartha S, Zhang S, Yu YH, Winkelstein B. The interface of mechanics and nociception in joint pathophysiology: insights from the facet and temporomandibular joints. *J Biomech Eng.* 2017;139:021003. https://doi. org/10.1115/1.4035647
- 90. Stemper BD, Yoganandan N, Gennarelli TA, Pintar FA. Localized cervical facet joint kinematics under physiological and whiplash loading. J Neurosurg Spine. 2005;3:471-476. https://doi. org/10.3171/spi.2005.3.6.0471
- 91. Sterling M, Hodkinson E, Pettiford C, Souvlis T, Curatolo M. Psychologic factors are related to some sensory pain thresholds but not nociceptive flexion reflex threshold in chronic whiplash. *Clin J Pain*. 2008;24:124-130. https://doi. org/10.1097/AJP0b013e31815ca293
- 92. Sterling M, Jull G, Vicenzino B, Kenardy J. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. *Pain.* 2003;104:509-517. https://doi.org/10.1016/ S0304-3959(03)00078-2
- 93. Sterling M, Kenardy J. Physical and psychological aspects of whiplash: important considerations for primary care assessment. *Man Ther*. 2008;13:93-102. https://doi.org/10.1016/j. math.2007.11.003
- 94. Sullivan MJ, Adams H, Martel MO, Scott W, Wideman T. Catastrophizing and perceived injustice: risk factors for the transition to chronicity after whiplash injury. *Spine (Phila Pa* 1976). 2011;36:S244-S249. https://doi.org/10.1097/ BRS.0b013e3182387fed
- **95.** Sundararajan S, Prasad P, Demetropoulos CK, et al. Effect of head-neck position on cervical facet stretch of post mortem human subjects during low speed rear end impacts. *Stapp Car Crash J.* 2004;48:331-372.
- 96. Tachihara H, Kikuchi S, Konno S, Sekiguchi M. Does facet joint inflammation induce radiculopathy?: an investigation using a rat model of lumbar

facet joint inflammation. Spine (Phila Pa 1976). 2007;32:406-412. https://doi.org/10.1097/01. brs.0000255094.08805.2f

- **97.** Takahashi Y, Nakajima Y. Dermatomes in the rat limbs as determined by antidromic stimulation of sensory C-fibers in spinal nerves. *Pain*. 1996;67:197-202. https://doi. org/10.1016/0304-3959(96)03116-8
- **98.** Tower TT, Neidert MR, Tranquillo RT. Fiber alignment imaging during mechanical testing of soft tissues. *Ann Biomed Eng.* 2002;30:1221-1233. https://doi.org/10.1114/1.1527047
- 99. Van Oosterwijck J, Nijs J, Meeus M, Paul L. Evidence for central sensitization in chronic whiplash: a systematic literature review. *Eur J Pain*. 2013;17:299-312. https://doi. org/10.1002/j.1532-2149.2012.00193.x
- 100. Velázquez KT, Mohammad H, Sweitzer SM. Protein kinase C in pain: involvement of multiple isoforms. *Pharmacol Res*. 2007;55:578-589. https://doi.org/10.1016/j.phrs.2007.04.006
- **101.** Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. *J Manipulative Physiol Ther*. 1991;14:409-415.
- **102.** Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2163-2196. https://doi. org/10.1016/S0140-6736(12)61729-2
- 103. Walker K, Bowes M, Panesar M, et al. Metabotropic glutamate receptor subtype 5 (mGlu5) and nociceptive function. I. Selective blockade of mGlu5 receptors in models of acute, persistent and chronic pain. *Neuropharmacology*. 2001;40:1-9. https://doi.org/10.1016/ S0028-3908(00)00113-1
- 104. Walton DM, MacDermid JC, Giorgianni AA, Mascarenhas JC, West SC, Zammit CA. Risk factors for persistent problems following acute whiplash injury: update of a systematic review and metaanalysis. J Orthop Sports Phys Ther. 2013;43:31-43. https://doi.org/10.2519/jospt.2013.4507
- 105. Weisshaar CL, Dong L, Bowman AS, et al. Metabotropic glutamate receptor-5 and protein kinase C-epsilon increase in dorsal root ganglion neurons and spinal glial activation in an adolescent rat model of painful neck injury. J Neurotrauma. 2010;27:2261-2271. https://doi. org/10.1089/neu.2010.1460
- **106.** Weisshaar CL, Winkelstein BA. Ablating spinal NK1-bearing neurons eliminates the develop-

ment of pain and reduces spinal neuronal hyperexcitability and inflammation from mechanical joint injury in the rat. *J Pain*. 2014;15:378-386. https://doi.org/10.1016/ j.jpain.2013.12.003

- 107. Winkelstein BA. How can animal models inform on the transition to chronic symptoms in whiplash? Spine (Phila Pa 1976). 2011;36:S218-S225. https://doi.org/10.1097/BRS.0b013e3182387f96
- 108. Winkelstein BA, Nightingale RW, Richardson WJ, Myers BS. The cervical facet capsule and its role in whiplash injury: a biomechanical investigation. Spine (Phila Pa 1976). 2000;25:1238-1246.
- 109. Winkelstein BA, Santos DG. An intact facet capsular ligament modulates behavioral sensitivity and spinal glial activation produced by cervical facet joint tension. *Spine (Phila Pa 1976)*. 2008;33:856-862. https://doi.org/10.1097/ BRS.0b013e31816b4710
- 110. Xu GY, Zhao ZQ. Change in excitability and phenotype of substance P and its receptor in cat Aβ sensory neurons following peripheral inflammation. Brain Res. 2001;923:112-119. https://doi. org/10.1016/S0006-8993(01)03203-6
- **111.** Yahia LH, Garzon S. Structure on the capsular ligaments of the facet joints. *Ann Anat.* 1993;175:185-188.
- 112. Yamashita T, Minaki Y, Ozaktay AC, Cavanaugh JM, King AI. A morphological study of the fibrous capsule of the human lumbar facet joint. *Spine* (*Phila Pa* 1976). 1996;21:538-543.
- 113. Yoganandan N, Pintar FA. Inertial loading of the human cervical spine. J Biomech Eng. 1997;119:237-240. https://doi.org/10.1115/ 1.2796086
- 114. Yoganandan N, Pintar FA, Cusick JF. Biomechanical analyses of whiplash injuries using an experimental model. *Accid Anal Prev*. 2002;34:663-671.
- 115. Zhang S, Cao X, Stablow AM, Shenoy VB, Winkelstein BA. Tissue strain reorganizes collagen with a switchlike response that regulates neuronal extracellular signal-regulated kinase phosphorylation in vitro: implications for ligamentous injury and mechanotransduction. J Biomech Eng. 2016;138:021013. https://doi. org/10.1115/1.4031975



### **DOWNLOAD** PowerPoint Slides of JOSPT Figures

*JOSPT* offers **PowerPoint slides of figures** to accompany all full-text articles with figures on *JOSPT*'s website (**www.jospt.org**). These slides are generated automatically by the site, and can be downloaded and saved. They include the article title, authors, and full citation. *JOSPT* offers full-text format for all articles published from January 2010 to date.

#### This article has been cited by:

1. Sijia Zhang, Vahhab Zarei, Beth A. Winkelstein, Victor H. Barocas. 2017. Multiscale mechanics of the cervical facet capsular ligament, with particular emphasis on anomalous fiber realignment prior to tissue failure. *Biomechanics and Modeling in Mechanobiology* **41**. [Crossref]