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The Interface of Mechanics and Nociception in Joint Pathophysiology: Insights From the Facet and Temporomandibular Joints

Chronic joint pain is a widespread problem that frequently occurs with aging and trauma. Pain occurs most often in synovial joints, the body's load bearing joints. The mechanical and molecular mechanisms contributing to synovial joint pain are reviewed using two examples, the cervical spinal facet joints and the temporomandibular joint (TMJ). Although much work has focused on the macroscale mechanics of joints in health and disease, the combined influence of tissue mechanics, molecular processes, and nociception in joint pain has only recently become a focus. Trauma and repeated loading can induce structural and biochemical changes in joints, altering their microenvironment and modifying the biomechanics of their constitutive tissues, which themselves are innervated. Peripheral pain sensors can become activated in response to changes in the joint microenvironment and relay pain signals to the spinal cord and brain where pain is processed and perceived. In some cases, pain circuitry is permanently changed, which may be a potential mechanism for sustained joint pain. However, it is most likely that alterations in both the joint microenvironment and the central nervous system (CNS) contribute to chronic pain. As such, the challenge of treating joint pain and degeneration is temporally and spatially complicated. This review summarizes anatomy, physiology, and pathophysiology of these joints and the sensory pain relays. Pain pathways are postulated to be sensitized by many factors, including degeneration and biochemical priming, with effects on thresholds for mechanical injury and/or dysfunction. Initiators of joint pain are discussed in the context of clinical challenges including the diagnosis and treatment of pain.
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Introduction

Chronic joint pain is a costly and widespread problem, affecting 110 million adults in the U.S. at some point over the course of their lifetime and having an estimated total cost of $60 million annually [1,2]. However, due to the complex relationships between joint mechanics, tissue degeneration, and nociceptive signaling of pain, effective treatments for joint pain are lacking [3–6]. The challenge of defining biomechanical, physiological, and pathological mechanisms of pain is further complicated by many confounding factors that are implicated in the origin and maintenance of joint pain. This complexity also impedes the effective diagnosis of the etiology of joint injury and osteoarthritis (OA) before permanent changes in joint structure and pain signaling occur [7–9].

Synovial joints permit complex motion and often sustain loads several times greater than the weight of the human body; yet, in some cases, repeated and mechanical loading above the normal physiological conditions contribute to the initiation of acute tissue damage and degeneration [10]. Further, the local mechanical environment of joints can be substantially altered after injury

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or degeneration, which, in some cases, produces dysfunctional nociceptive signaling [11–14]. Neck pain is among the most prevalent chronic joint pathologies, with 30–50% of the adult population reporting pain over a 12 month period [6]. Jaw pain is also a widespread musculoskeletal condition, affecting 5–12% of the population [1]. Neck pain is most often induced by trauma and can involve damage, like loading and stretching of the facet capsular ligament, to the bilateral facet joints that provide articulations between spinal levels [15,16]. In addition, neck pain can also result from nontraumatic, cumulative exposures, such as sustained neck flexion postures [17]. Innervated by mechanoreceptors, disruption of the collagen fibers that make up the facet capsular ligament can initiate nociceptive signaling and lead to both acute and chronic pain [14,18–20]. By comparison, jaw pain is less often caused by trauma and is typically initiated by repeated atypical loading of the temporomandibular joint (TMJ) that leads to inflammatory cascades within the synovium and that can sensitize pain fibers in the joint [8,9]. Accordingly, mechanical injury can disrupt the normal microenvironment of joint tissues in several distinct ways, including via acute traumatic loading and/or stretching of the capsular ligaments of the joint or by repeated, nontraumatic loading to the tissues in the joint. Both traumatic and repeated mechanical disruption can induce structural changes to joint tissues and inflammatory cascades, which separately activate pain fibers via a modified biomechanical and biochemical environment [13,21–23].

Pain is an unpleasant sensory and emotional experience that occurs when there is potential for tissue damage to occur [24] or in response to an inciting injury as from OA [25]. In both cases, pathophysiological tissue loading triggers both peripheral and central nociceptive signaling cascades that initiate and sustain pain [25,26]. By distinction, the term "nociception" specifically refers to the physiological responses and signal transmission that encode pain [24]. Although peripheral nociceptive neurons are critical to the encoding and transmission of pain signals, the *experience* of pain includes both sensory and emotional components, as modulated by specific brain regions (and reviewed comprehensively elsewhere [27]). Human chronic pain can also occur in the absence of nociceptive input or tissue damage [28]; however, this review focuses on cases in which nociceptive pain is present. Since the combination of sensory, emotional, and cognitive aspects of pain contributes to the complexity of chronic pain, differentiating the relative contributions of biomechanical factors on different cells involved in the pathomechanisms of pain and injury is needed to understand and treat this complex disease.

Nociceptive neurons are pseudo-unipolar cells, with their cell body in the dorsal root ganglion (DRG) and axonal projections that innervate peripheral tissues and others that extend to the central nervous system (CNS) to transmit information to the brainstem, thalamus, and cortex of the brain. Accordingly, nociceptive signals from a joint are communicated via peripheral nerves through the DRG and are subsequently modulated by phosphorylation of intracellular kinases, synaptic receptors, and ion channels in the spinal cord and brainstem [29–31]. The thalamus receives signals from the spinal cord and brainstem, and projects information to cortical and limbic structures for further processing and signal interpretation [27]. Repeated stimulation of afferent fibers, such as those that can occur by repeated tissue loading or abnormal joint kinematics, can lead to neuron sensitization, which is an increased responsiveness to otherwise normal or typically subthreshold inputs [24,32]. In the periphery, sensitization manifests as altered nociceptive responses in the neurons in and around joints, with their activation at decreased thresholds and their increased responsiveness to stimulation [26,32]. Central sensitization in the spinal cord and brain produces sustained neuronal hyperexcitability, amplification of signals from peripheral sources, increased spontaneous activity, and reduced thresholds for activation, as well as plastic rewiring of the neuronal circuitry in and between the spinal cord and brain [24,26,33–35]. Collectively, these changes in neuronal signaling can lead to persistent pain even in the *absence* of any on-going tissue damage or input from peripheral nociceptive fibers [26,29].

Using the spinal facet joints and TMJ as models of pain from biomechanical mechanisms, this review attempts to summarize the current understanding of pathobiomechanical mechanisms that initiate and sustain joint pain in the peripheral and central nervous systems. It also integrates outcomes from experiments performed across cellular, tissue, and system scales, as well as proposes possible future directions for mechanistic investigation and diagnostic imaging. The review begins by highlighting relevant joint anatomy and pain mechanisms associated with dynamic loading of the spinal facet joint and repeated compressive loading of the TMJ. These two joints are highlighted for their similarities and also for the unique differences in which pathomechanisms are initiated. Tissue mechanics and neurobiological aspects of joint pain are integrated in discussions of the macro- and micromechanics of both joint tissues, degeneration, and priming of afferent nociceptors. Finally, current and emerging imaging techniques to assess early functional modifications in both joint tissue and pain circuitry of the CNS are presented.

Mechanical Injury of the Facet Capsular Ligament

The facet joints are bilateral joints located in the posterolateral region of the spine and that are responsible for providing mechanical load transmission and motion coupling throughout the full spine (Fig. 1) [22,36]. The cervical facet joint is composed of hard and soft tissues that together not only couple rotation during bending in the neck, but also transmit axial load [22,37]. The bony articular pillars that extend laterally from vertebral laminae are covered by articular cartilage and provide the opposing surfaces with frictionless surfaces to enable the smooth articulation of the joint [38,39]. The membranous synovium lines between those articular surfaces and folds into the joint space to form meniscoids that protect the articular cartilage during joint movement [40]. The facet capsular ligament encloses the articulating bones of the facets of adjacent vertebrae creating a joint space [41–43]. That ligament is composed of crimped collagen fibers which permit substantial stretch and has a large degree of laxity to permit extensive ranges of spinal bending and rotation without mechanical resistance or failure [41].

The facet capsular ligament is innervated by mechanoreceptors that encode movement and stretch, and also by nociceptors that encode nociceptive stimuli [44–46]. Disruption of the facet capsule and other innervated tissues in the facet joint can elicit pain [44,45,47–51]. Trauma to the facet joint, as can happen by direct stretch of the facet capsule or compressive loading of the joint, can result from traumatic spine loading [52–57] and imposes excessive deformation and abnormal kinematics in the facet joint. Such mechanical injury to the facet joint can occur as the spine undergoes altered kinematics which induce excessive joint motions and/or combined loading to its tissues, as can occur when the head is axially rotated and the spine is pretorqued while the neck undergoes flexion-extension loading [57]. Dynamic spinal loading can pinch the synovial meniscoids and produce microstructural damage in the facet capsular ligament, both of which have the potential to alter the biochemical and mechanical microenvironment of the facet joint and to initiate osteoarthritic degeneration [11,19,55]. After such trauma or injury to the facet joint, patients often present with complex pain symptoms that include both physical and psychological components, with localized and widespread evoked pain, spontaneous pain, and/or psychological disturbances [58–60]. Existing psychological distress may also contribute to the maintenance of pain [60].

Although several forms of spinal loading can directly or indirectly activate the afferent fibers that innervate the facet joint structures, excessive stretch of the facet capsular ligament, in particular, induces persistent pain and modifications in neuronal signaling [18,61,62]. Peak facet capsular ligament strains of 35.4% have been observed during traumatic cervical spine loading

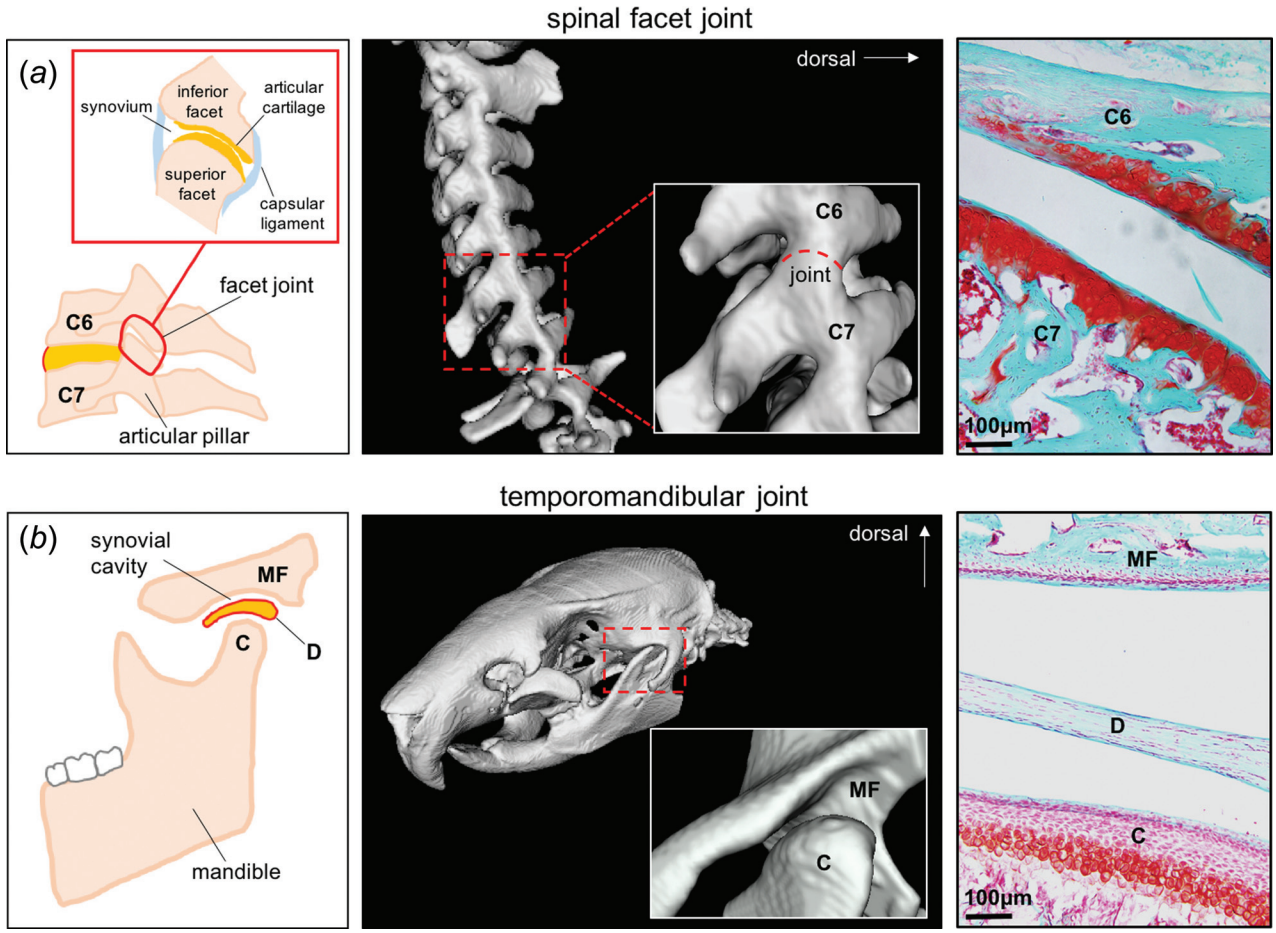

Fig. 1 Human anatomy and rat computed tomography (CT) three-dimensional reconstructions and Safranin-O staining of tissue sections of the (*a*) facet joint and (*b*) TMJ, with important anatomy highlighted: sixth cervical vertebrae (C6), seventh cervical vertebrae (C7), mandibular fossa (MF), articular disk (D), and mandibular condyle (C)

in vitro [54], implicating mechanical damage of this ligament in pain production. Facet capsule stretch imposed by in vivo distraction of the joint in the rat produces strains below the failure limit of that ligament but that exceeds the normal physiologic range of stretch and induces chronic pain [61,63,64]. The magnitude of capsular stretch has been identified as a key modulator of the onset and maintenance of pain, with the supraphysiologic strains known to induce pain defined as those above 8–10% [63,65]. Furthermore, the severity of the sustained behavioral hypersensitivity (i.e., pain) is significantly correlated with the applied facet capsule strain [63,65]. However, complete capsule rupture, which likely also fully transects the pain fibers embedded in the facet joint, does *not* initiate chronic pain [61], suggesting a critical role of *intact* peripheral afferents in either transmitting nociceptive information to the central nervous system or in their dysfunction modulating the extensive pain system. Interestingly, such a notion highlights the complexity of this pathophysiology in that failure of this ligament is not "worse" in terms of initiating pain cascades, despite such tissue failure possibly leading to long-term alterations in the mechanical properties of that joint due to tissue scarring and/or degenerative cascades [22].

Facet joint pain in rodent models mirrors the temporal and spatial features of evoked pain in humans, emerging within hours after injury and lasting for several weeks to years in patients [66–68]. However, it should be noted that issues of scaling between the anatomic size and shape, magnitudes of loading, and relative age between animals and humans make it challenging to draw direct comparisons between species. Nevertheless, the similarities in the biomechanical metrics between human cadavers and rodents, as well as consistency between pharmacologic treatments on physiologic responses in rodents and humans, support the strengths of this work. In rodent models, excessive strains applied to the facet capsule lead to pain onset in between 6 h and 1 day which persists for up to 28 days [34,35,69,70]. The widespread hypersensitivity that patients experience following cervical spine trauma [68,71] is also detectable at the shoulders and forepaws in the rat after similar facet joint injury [61,63,72]. Although the capsular ligament is a critical mediator of pain and disability in cervical spinal trauma, pathologies in other synovial joints, such as the TMJ, may be driven by different modes of mechanical loading, including repeated compression of articular cartilage and subchondral bone [9].

Osteoarthritic Pathology of the Temporomandibular Joint

Similar to the spinal facet joints, the TMJs are synovial joints that undergo repeated physiologic loading and, in some cases, are subjected to pathological overloading. The TMJs connect the mandible to the temporal bone of the skull, permitting normal mouth opening and closing [8] (Fig. 1). The TMJ is separated into two compartments by a fibrocartilaginous articular disk surrounded by synovial fluid (Fig. 1) [73,74], which allows the mandibular condyle to articulate smoothly with the glenoid fossa of the temporal bone [8]. Since normal jaw opening imposes rotation and anterior translation of the condyle in the glenoid fossa and posterior translation of the articular disk, many different anatomic tissues experience complex local mechanical environments [8].

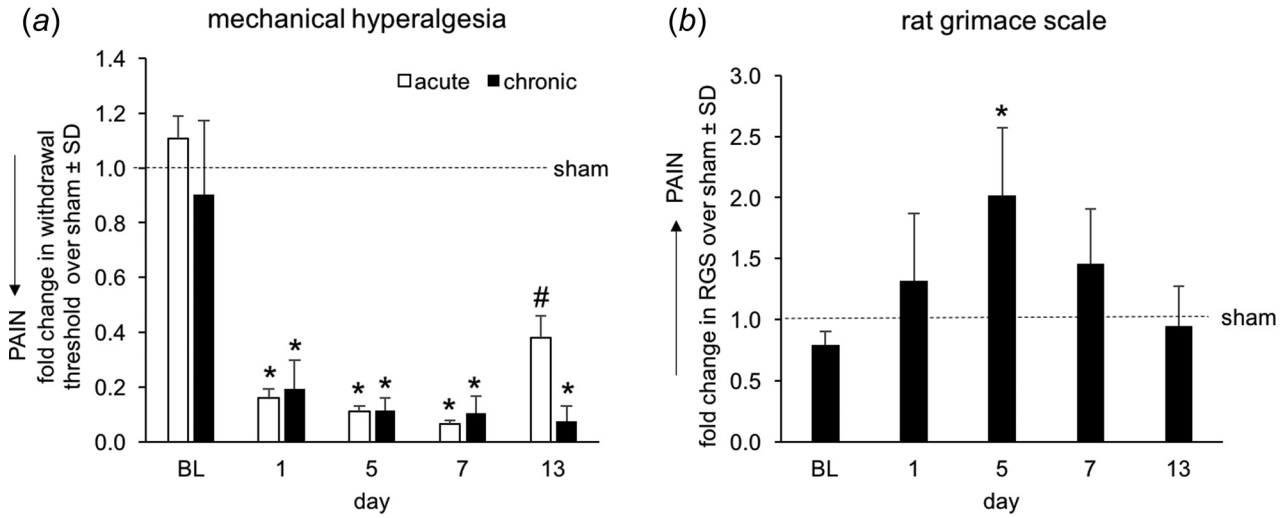

Fig. 2 Behavioral measurements of pain in the area of the TMJ using techniques to (*a*) measure mechanical hyperalgesia and (*b*) quantify the rat grimace scale scoring for spontaneous pain levels. Both behavioral responses are shown relative to sham control responses receiving only exposure to anesthesia. For both assessments, a one-way ANOVA compared groups ($n = 4$/group), with the chronic exposure being different from the sham response (*$p < 0.001$; #$p = 0.015$). Baseline (BL) measurements are taken before any exposures and also serve as a control measurement.

Injury or degeneration of any of the bone, cartilage, or disk in the TMJ can affect jaw movement, joint morphology, and, in some patients, lead to pain [8,9].

Clinically, TMJ disorder presents with many different disease pathologies, including pain in the TMJ, limited or asymmetric jaw motion, and/or TMJ sounds that are associated with motion [75,76]. Although TMJ disorders often have complex etiologies, the most common pathology affecting the joint is OA [77]. OA is often associated with parafunctional habits, such as jaw clenching [75], that increase mechanical loads on the mandible [78]. Functional overloading of the mandible can cause dysfunctional remodeling, abrasion of articular cartilage, and low-grade inflammation in the joint [77,79]. These pathological changes activate the nociceptive neurons of the trigeminal nerve that innervate bone, synovial tissue, ligaments, muscles, and capsular tissues in the TMJ [80]. For the vast majority of patients, TMJ disorder is self-resolving and requires little to no treatment. However, approximately 15% of patients develop a nonresolving, chronic form of TMJ pain that is recalcitrant to therapy, with associated physical, behavioral, and psychological symptoms [1,8]. Similar to chronic neck pain from spine trauma, human and animal studies suggest that persistent TMJ pain is due to augmented central pain processing mechanisms [60,81–85].

Abnormal TMJ loading and the associated orofacial pain have been simulated by repeated mouth-opening in the rodent [13,86]. TMJ loading reorganizes cartilage and is associated with upregulation of biochemicals involved in OA, such as vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α) [13,86,87]. Application of different loading magnitudes to the jaw, for 1 h per day for 7 days, induces distinct pain responses in the rat, suggesting a correlation between the loading magnitude and pain (Fig. 2(*a*)). Evaluating mechanical hyperalgesia, an increased response to stimulation, demonstrates that a 2 N load to the jaw produces acute TMJ hyperalgesia that resolves to baseline (BL) levels by day 14, while a 3.5 N load induces chronic TMJ hyperalgesia, with sustained pain for up to 28 days [13,86]. However, mechanical hyperalgesia does not measure spontaneous pain, which is an important clinical outcome and is influenced by both sensory and affective components [88]. In rodent models, spontaneous pain can be measured by evaluating facial expression using the rat grimace scale (RGS) [88,89]. Preliminary studies demonstrate a substantial increase in RGS scores at day 1 after 3.5 N loading, significantly greater pain at day 5 than sham controls with no loading, and a return to sham levels by day 13 (Fig. 2(*b*)). Elevated RGS scores and mechanical hyperalgesia indicate that both sensory *and* affective components of pain may be implicated in mechanical TMJ pain. Despite the association between certain magnitudes of TMJ loading and chronic pain, the mechanisms by which abnormal mechanics disrupts pain signaling remain unclear. Recent evidence from the same model suggests that hypoxia and inflammation increase in the TMJ after joint loading, with upregulation of HIF-1α, VEGF, matrix metalloproteinases (MMPs) [13]. These outcomes are associated with degenerative pathologies in humans [90] and in other animal models [91–93], suggesting that TMJ nociceptors may be sensitized by degenerative molecules and enzymes as a result of TMJ loading.

Pain and Mechanical Dysfunction in Degenerated Joints

Degenerative joint pathologies, such as OA, are initiated by a complex combination of applied mechanical loads and biological cascades within the joint's tissues [13,92,94,95]. Both trauma and age contribute to joint degeneration [96]' yet, the mechanisms by which pain is initiated in degenerative joints are still unclear [97–100]. The facet joints are susceptible to degeneration from supra-physiological mechanical loading and/or injury [101,102]. Further, animal models of facet joint degeneration induced by intra-articular delivery of collagenase or complete Freud's adjuvant (CFA) induce inflammation, loss of cartilage, osteophyte formation, and subchondral bone changes in the joint [94,103], and suggest that such changes may be involved in joint degeneration. In vivo studies also support that similar degenerative mechanisms may occur in the TMJ; loss of articular cartilage and remodeling of subchondral bone are reported in response to mechanical loading and intra-articular injection of CFA [13,81,86,87,104]. In particular, in degenerative TMJs, the intra-articular cartilage exhibits increased expression of VEGF, HIF-1α, and tumor necrosis factor (TNF) in the hypertrophic and mature cartilage layers [13,81,87]. Expression of MMP-13, a protein involved in collagen matrix restructuring, also increases in the TMJ after its loading [13,105], demonstrating a connection between mechanical loads and enzymatic microdamage in the TMJ articular cartilage. Sustained expression of these and other degenerative and inflammatory factors leads to cartilage thinning and changes in the underlying bone that can compromise the mechanical integrity of the overall

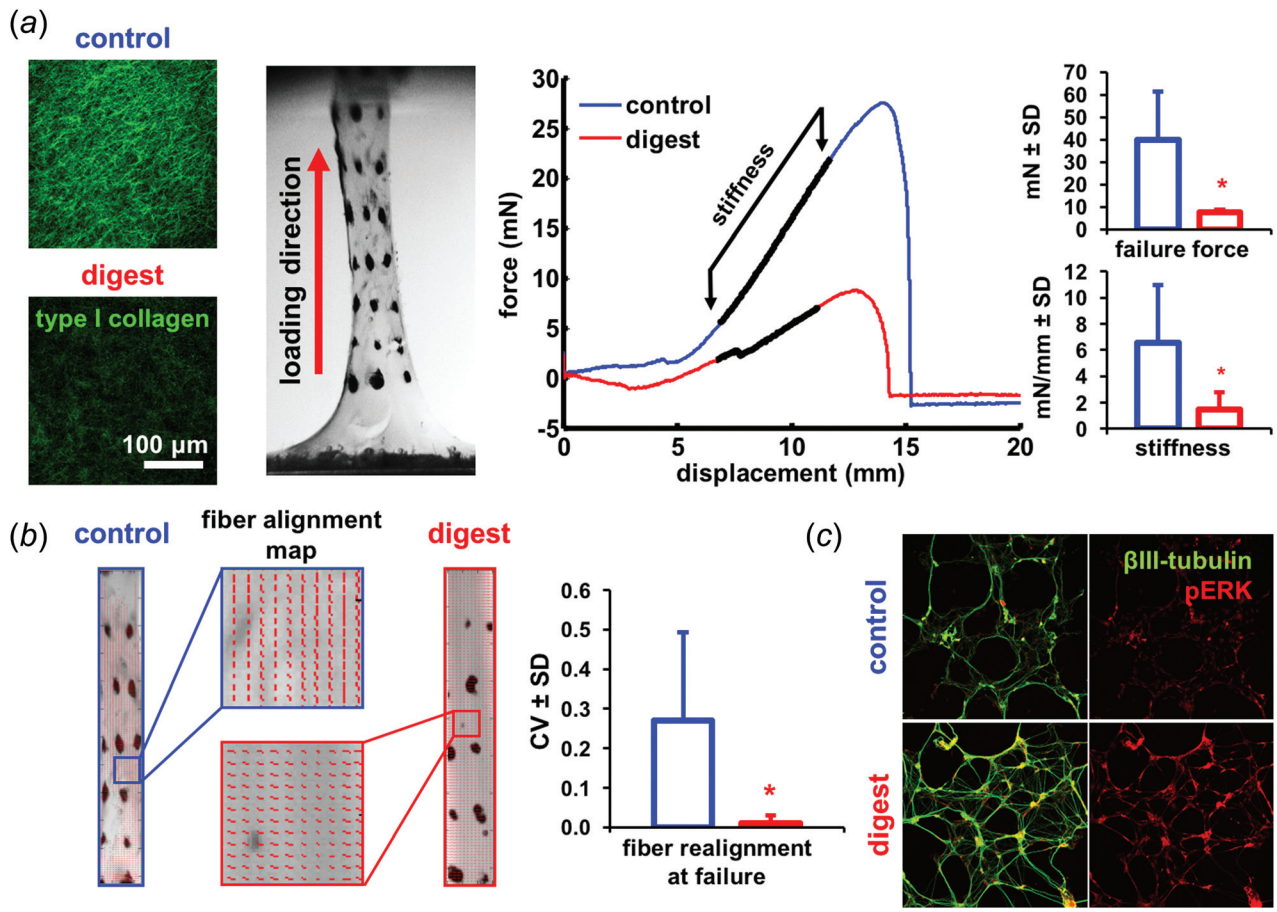

Fig. 3 Collagenase digestion of an in vitro collagen gel system shows that collagenase digestion that is sufficient to (*a*) reduce collagen fiber content also decreases the failure force (*$p = 0.007$) and stiffness (*$p = 0.024$) of the gel when loaded in tension, (*b*) The microstructural collagen fiber reorganization at failure in the gel under tension is also altered, with the normal reorganization of collagen fibers that is evident at failure being absent and a lower circular variance (CV) (*$p = 0.001$). A higher CV value indicates fiber realignment toward the loading direction, and (*c*) The same collagenase treatment also increases the expression of phosphorylated ERK (pERK) after loading in mixed neuronal cultures.

joint and its tissues, increasing their susceptibility to mechanical injury [106].

Tissue degeneration is driven by enzymes that degrade the individual tissues and alter the mechanical and biochemical properties of the overall joint [22,107]. Enzymes like MMPs and a disintegrin and metalloprotease with Thrombospondin motifs (ADAMTSs) degrade the collagen, aggrecan, and proteoglycans that compose the extracellular matrix [108,109]. Loss of these structural proteins specifically compromises the articular cartilage and capsular ligament [108–110]. Selective digestion of constitutive components of the extracellular matrix, such as collagen, elastin, or proteoglycans, can change ligament structure by inducing crimp [111], decreasing stiffness [112], and increasing cartilage deformation in response to loading [113]. In vitro collagenase digestion that is sufficient to reduce collagen immunolabeling by 47% in a collagen gel system also decreases the stiffness ($p = 0.024$) and failure force ($p = 0.007$) of the gels under uniaxial tension to failure (Fig. 3(*a*)). Furthermore, that loss of collagen also results in less microstructural fiber reorganization during gel stretch, with fewer collagen fibers reoriented along the direction of loading compared to undigested control gels ($p = 0.001$) (Fig. 3(*b*)). These changes in the macroscale mechanics of collagenase-digested gels are consistent with altered mechanics of enzyme-digested native joint tissues [94,114]; both demonstrate that enzymatic reduction of constitutive matrix components compromises biomechanical behavior. Together, these studies suggest that degenerated joint tissues may have lower thresholds for mechanical injury. At the very least, it is likely that degenerated joint tissues respond differently to loading than healthy counterparts. A clinical study reported ligament tearing and fibrillation without any direct traumatic injury in patients with early signs of cartilage degeneration [115].

Since the local biomechanical environment of neurons mediates their nociceptive signaling [14,116,117], and degeneration-associated tissue degradation alters the biomechanical environment of innervated joint tissues [22,111,115], degeneration may also lower thresholds for painful injury. This notion is supported by studies demonstrating that strains that induce microstructural damage correspond to those strains that induce pain in vivo and activate neurons embedded in collagen networks in vitro [11,14]. Collectively, in vitro studies suggest a relationship between the initiation of nociceptive signaling and the onset of microstructural damage, at least in capsular ligaments. Although abnormal kinematics initiate pain signaling [63,118] and degeneration alters tissue mechanics [22], excessive stretch or mechanical injury is not *required* for degeneration-induced pain. For example, there is not a direct correlation between the amount of structural damage (i.e., osteophytes, bone cysts, and meniscal changes) and pain levels in patients with knee OA [119]. This disconnection between pain and apparent tissue damage suggests that other molecular pathways, like inflammatory cytokines and chemokines, may be altered in the degenerative state and may more directly play a role in pain generation; indeed, inflammatory factors have been detected in the synovial fluid of OA patients [90,120].

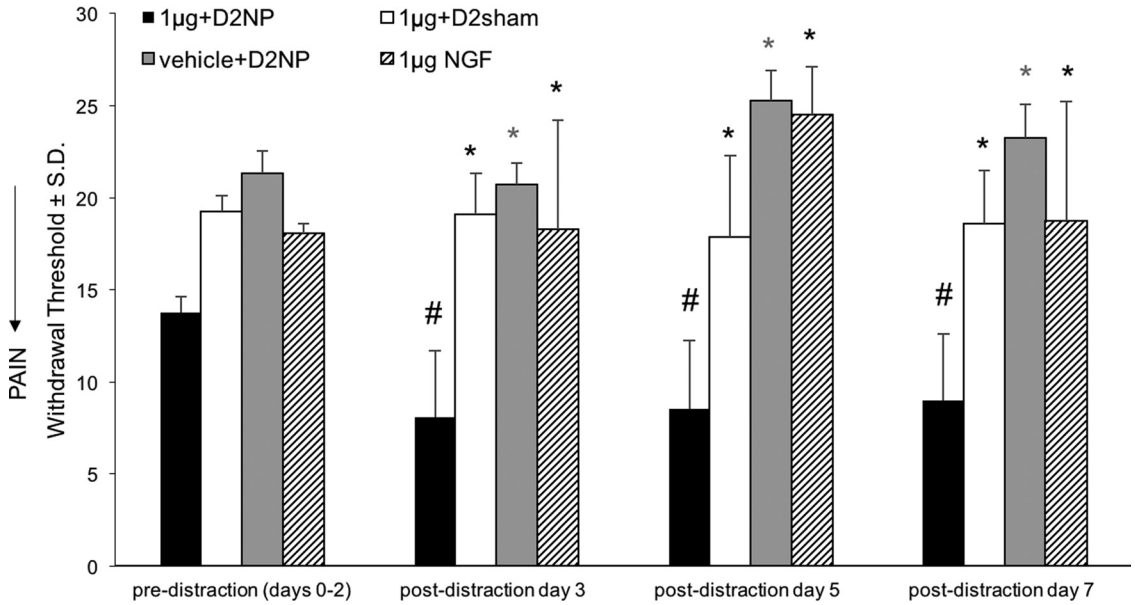

Fig. 4 Intra-articular NGF injection prior to physiological facet joint loading induces pain, with decreased withdrawal thresholds from baseline (#$p < 0.001$). The groups receiving only 1 μg of NGF or a nonpainful distraction (vehicle + D2NP) does not develop pain and their withdrawal thresholds are greater than the group receiving NGF prior to physiological loading. (1 μg + D2NP) (*$p < 0.05$).

Several other biochemical molecules involved in the degenerative cascades may act as neuronal "sensitizers" to initiate nociception. Collagenase induces features of OA degeneration in facet and knee joints [94,121]. Yet, its effects on neuronal sensitization and pain development are still undefined. Despite this, applying collagenase to mixed cell cultures of dissociated dorsal root ganglia increases neuronal expression of phosphorylated extracellular signal-regulated kinase (pERK), a signaling molecule and indicator of neuronal activation (Fig. 3(*c*)). Activation of ERK signaling in neurons can produce sustained hyperexcitability and altered signaling [50,122]. The increase in neuronal pERK after collagenase exposure suggests that it may have properties of direct sensitization; however, more work is needed to identify the degenerative molecules that most sensitize neurons.

Afferent Priming in Mechanically Induced Joint Pain

Although degeneration has been linked to changes in the joint biomechanics, inflammatory status, and pain, the microenvironment of a joint or the spinal cord can be altered by biochemical mediators that lead to increased nociceptive signaling. Transient insults to primary afferent nociceptors can produce sustained changes in neural transmission that can increase the constellation of nociceptive responses that are induced by later *subthreshold* insults (which are normally insufficient to evoke pain) [123–125]. For example, exposure to a single stimulant such as carrageenan or TNF produces only transient pain in the rat, while secondary stimulation with an inflammatory mediator (i.e., prostaglandin PGE_2) induces persistent pain [126,127]. In addition to inducing pain, priming of afferent nociceptor populations can induce plastic changes in the CNS [125] that further increase susceptibility to later develop chronic pain.

Pain development is, in part, driven by the upregulation of nociceptive molecules, such as nerve growth factor (NGF) [23,128,129]. NGF is upregulated early after the induction of painfully inflamed and arthritic joints, with similar timing to inflammatory cytokines, and is responsible for the development, proliferation, and survival of neurons [130,131]. When delivered to a joint at sufficient concentrations, it can induce mechanical and thermal hypersensitivity, as well as spinal neuronal hyperexcitability, particularly in peptidergic afferents [23,129]. Accordingly, intra-articular NGF levels may be important in the onset of pain after facet joint trauma due to the high proportion of peptidergic afferents [132] and expression of the NGF receptor, trkA, in the facet joint [133]. Increased NGF accompanied by inflammation has been shown to contribute to the pain and spinal glial activation and neuronal hyperexcitability that develop after trauma to the facet joint [20,23,134]. Moreover, delivery of anti-NGF treatment to joints early after their injury blocks the development of pain [23,135], suggesting that NGF has a role in the *initiation* of pain. However, delaying anti-NGF administration until after pain has developed is ineffective in attenuating either pain or spinal neuronal hyperexcitability [23]. NGF appears to be an intra-articular initiator of joint injury-induced pain, but not involved in pain *maintenance*. Based on these findings, it is also possible that elevated levels of NGF may sensitize nociceptors, making them more susceptible to activation at lower thresholds upon future mechanical loading.

Intra-articular injection of NGF at concentrations below that which induces pain when given alone [23,128] was used to investigate if NGF increases the risk for pain from a normally non-painful physiological facet ligament stretch. NGF was injected into the bilateral C6/C7 facet joints at a dose of 1 μg in 5 μL of sterile phosphate buffered saline (PBS); 2 days after that injection, rats received either a nonpainful physiologic facet joint distraction (1 μg + D2NP; $n = 6$) or a sham surgery procedure (1 μg + D2sham; $n = 6$) [63,136,137]. Control groups were also included with a vehicle group receiving only PBS followed by a nonpainful distraction on day 2 (vehicle + D2NP; $n = 6$) and an NGF injection-only group (1 μg NGF; $n = 6$) with no joint loading. Pain was induced in the group having prior intra-articular NGF exposure, with significantly lower withdrawal thresholds than before distraction ($p < 0.0012$) for each day after loading (Fig. 4). Withdrawal thresholds for that group are also significantly lower ($p < 0.0278$) than any of the other groups on all days after physiological loading (Fig. 4). This pilot work suggests that, in some cases, large modulation in the biochemical milieu of the joint may not be required for pain to be initiated, especially if there are altered joint kinematics. Of note, if priming mechanisms, like elevated levels of NGF, indeed

sensitize joint nociceptors to physiologic joint loads, then this may explain why patients who undergo moderate loading of the neck develop persistent pain symptoms [60]. Current treatments for neck pain do not target many of the potential priming mechanisms that may lead to persistent pain [60]. Developing new interventions possibly targeting molecules that can sensitize joint afferents may offer novel treatments for people who develop pain after sustaining multiple minor neck injuries. However, since it is unlikely that there is *only* one mediator of nociceptor sensitization, particularly across different joint pathologies, additional in vivo and in vitro studies with varied mechanical inputs may be required to define the role of other molecules in nociceptor sensitization.

Integrating Macro- and Microscale Mechanics For Nociceptive Activity

Complex mechanical loading exceeding the physiologic range of a given joint can lead to persistent pain that arises from many structures in that joint [13,22,64,138]. In the neck, the facet capsular ligament is particularly vulnerable to excessive spinal motions because of the potential for ligament stretch to activate the nociceptors innervating that ligament [15,21]. The facet capsule is composed of complex multiscale fibrous structures, along with nonfibrillar materials and cells that also regulate its mechanical behavior [22,42,48]. Traumatic spinal loading, including shear, compression, and bending, can cause the facet ligament to undergo subfailure loading that produces injury, or even its failure [19,57,139–141]. Excessive stretch of the facet capsules is a common injury mechanism that produces highly heterogeneous deformations in that ligament at different spinal levels and a nonuniform strain field across individual ligaments [22,54,142]. Simulations of neck trauma using in vitro cadaveric systems indicate that horizontal acceleration can produce peak strains ($\sim$30%) in the C6/C7 facet capsule [54], corresponding to those strains that are sufficient to produce localized altered collagen fiber kinematics and sustained pain [63,142,143]. Although cadaveric testing accurately simulates and defines the macroscopic mechanical responses and microstructural changes of the human facet joints to spinal loading, it can neither fully capture microscopic mechanics nor assess any *physiological* cellular responses. Nevertheless, the biomechanical and structural metrics defined by cadaveric testing, such as ligament strain, disk compression, and motion segment kinematics [22,53,57], can be used in computational, cell culture, and in vivo animal model systems to further refine our understanding of the relationship between mechanics and physiology [14,15].

The relationship between mechanics and nociception can be directly measured by neurophysiologic responses that correlate with the applied stress and strain in isolated joint capsules [144]. In fact, the same magnitude of capsule strain that induces pain has been shown to separately activate the afferents that innervate the facet capsular ligament during and after capsule stretch in vivo [45,51,63,64]. Physiologic strains of 10–15% only activate mechanoreceptors, whereas strains greater than 25% trigger the activation of mechanoreceptors, produce sustained afterdischarge, and induce morphological changes in axons, including local swelling and vacuolations [51,145]. Although in vivo and ex vivo experiments provide evidence for a link between loading and mechanoreceptor activation, additional studies are required to elucidate this complex relationship.

Recent development of an in vitro neuron-collagen culture system has demonstrated that neuronal expression of pERK is correlated with the applied regional strain in the collagen matrix that surrounds neurons [14]. As the applied macroscopic strain increases, neuronal release of pERK increases substantially at strain levels that simultaneously induce collagen fiber reorganization [14]. Since strains associated with pain in vivo produce fiber realignment and elevate pERK in vitro, local peripheral biomechanics appear to align with tissue-level deformations and modulate neuronal responses that drive the development of pain. However, unlike in vivo experiments, in vitro systems can decouple the effects of inflammation, mechanics, and matrix structure on neuronal responses and enable simultaneous measurement of local strains, microscopic fiber kinematics, and cellular behaviors in response to macroscopic tissue deformation. Based on the relationships between multiscale mechanics and neuronal signaling in the facet capsule after its loading [14,51,63], it is possible to develop new in vitro models of injury. Such models enable modification of relevant mechanical and structural parameters to both understand pathomechanisms and potentially identify novel therapeutic targets that may be involved in the mechanotransduction pathways. Furthermore, the identification of critical pathomechanisms could be helpful also in developing predictive diagnostics for joint pathologies. Currently, clinical imaging collects structural information about joints, but provides little information about *active* biochemical processes. Therefore, outcomes from in vitro culture systems that relate joint mechanics and biochemical mediators could be an important source of information for developing clinical imaging techniques for pain.

Predictive Diagnostics in Joint Pathologies

Clinical imaging of joint pathology primarily focuses on joint anatomy to diagnose and predict patient outcomes [8,146], and does not capture active cellular processes that occur in response to joint loading and/or degeneration [8,9]. For example, patients presenting with TMJ pain are frequently screened with panoramic radiographs, and more recently, cone beam computed tomography (CBCT), an imaging technique that provides three-dimensional views of dental structures, to assess structural damage in the TMJ [8]. Anatomical signs of late-stage TMJ OA, such as erosions and osteophytes, can be identified by CBCT with high diagnostic accuracy [7,147]. Similar hallmarks of facet joint OA, including erosion of subchondral bone, cysts, joint space narrowing, and osteophytes [148], are detectable in the facet joint by CT and magnetic resonance imaging (MRI) [46,146,149,150].

Architectural changes to subchondral bone are also present in animal models of OA and are detectable by CT. Notably, alterations to bone and cartilage can be seen at early time points (2–5 weeks) in these models due to the high resolution of microCT imaging (resolution < 0.1 mm) and intensity of the model compared to clinical pathology. In the rat, 1 week of TMJ loading produces structural modifications to the TMJ condyle at day 14, which is 7 days after cessation of joint loading. Three-dimensional reconstruction of CT scans, obtained at day 14, demonstrate mild flattening of the condyle in the 3.5 N load model that produces chronic pain (Fig. 5(*a*)). Image subtraction between normalized scans at day 14 and baseline shows significant changes in CT image intensity in the chronic pain model compared to joints that were not loaded (Fig. 5(*b*)). However, there is no difference between the chronic and acute (2 N loading) pain models, suggesting that morphological changes alone may not drive persistent pain from TMJ loading. This is in accordance with clinical data that shows minimal flattening of the TMJ condyle in 35% of asymptomatic people [151].

The disconnection between anatomical disruption and joint pain is also reported in MRI studies of joint pathology in humans, including signs of disk displacement in *both* asymptomatic patients as well as patients with painful TMJs [152,153]. However, signs of disk displacements without reduction, in which the disk remains displaced with jaw opening, are more strongly associated with progressive TMJ dysfunction and pain compared to reducing disk displacements, in which the disk returns to a normal position during mouth opening [154]. Although some morphological changes, such as osteophytes and bone degeneration [79], are clinically relevant, many cases of disk displacement may be normal anatomic variants [153]. Functional imaging techniques, such as positron emission

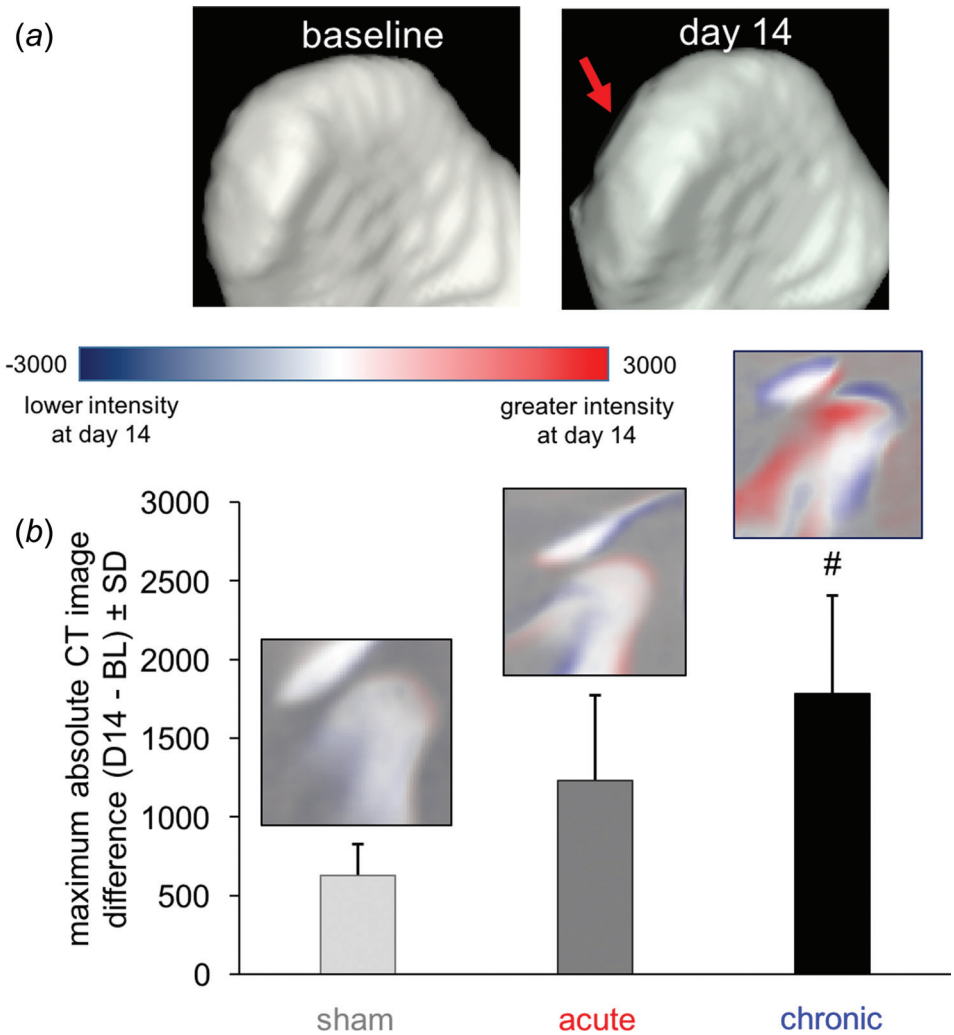

Fig. 5 In vivo CT imaging of the TMJ showing changes in the overall joint architecture, with (*a*) more flattening of the TMJ condyle at day 14 with chronic pain than for sham controls and (*b*) quantification of changes in bone density. Changes in the CT image intensity at day 14 by image subtraction from baseline (BL) show the greatest change from controls in TMJ condyle structure with chronic pain (#$p = 0.013$).

tomography (PET) and specific MRI sequences, may be able to better differentiate healthy from pathological joints and aid in earlier diagnoses [155,156]. For example, PET imaging with specific tracers, such as ^{18}F-FDG, a glucose analog, may enable measurement of synovitis. In the rat, FDG uptake is increased in an inflammatory arthritic knee joint compared to a contralateral control joint [157]. Patients with knee OA also have increased ^{18}F-FDG uptake in the affected joint compared to controls [156]; however, the association between tracer uptake and clinical presentations remains unclear. The uptake of the PET tracer sodium fluoride, ^{18}F-NaF, a marker of bone perfusion and metabolism, is increased in the affected joint of patients with TMJ OA, albeit with substantial variability between patients [155]. Similar outcomes are also identified using ^{99}Tcm hydroxymethylene diphosphonate single-photon emission computed tomography (SPECT) imaging of metabolic activity in bones of the TMJ [158]. Notably, metabolic activity of the bone does not correlate with pain scores [158], suggesting that bone activity is not strongly associated with joint nociception.

MRI, a nonradiative technique, is of particular clinical interest for imaging the joint synovium because it captures soft tissue morphology and water content. As such, novel MRI sequences for detecting particular pathologies are an active area of research [159]. Markers of active joint pathology, including synovitis, joint effusion, and interspinous ligament edema, are detectable in facet injury using fat-saturation and suppression MRI techniques [160,161]. These techniques may also be relevant to TMJ disorders, since a recent investigation using contrast-enhanced fat-suppression MRI reveals a correlation between contrast enhancement in the posterior disk attachments and severity of TMJ pain [162]. Ultrasound may also be capable of detecting active joint pathology, including synovial thickening and joint effusion, since ultrasound-detected markers of hand OA are significantly correlated with disease progression at 2 and 5 year follow-up exams [163,164]. However, the predictive value of these markers has not been verified in other joints. Despite the promise of imaging techniques that monitor the biochemical status of the joint, means for clinically measuring nociceptive dysfunction related to joint pathology are largely unstudied.

Functional brain imaging, including PET, fMRI, and diffusion tensor imaging (DTI), permit investigating functional and structural modifications of the CNS. Instead of solely relying on structures in the periphery, functional brain imaging can measure changes in neuronal activity and connectivity associated with pain [165–167] and, perhaps, predict the likelihood of transition to chronic pain. Clinical investigation using fMRI techniques shows

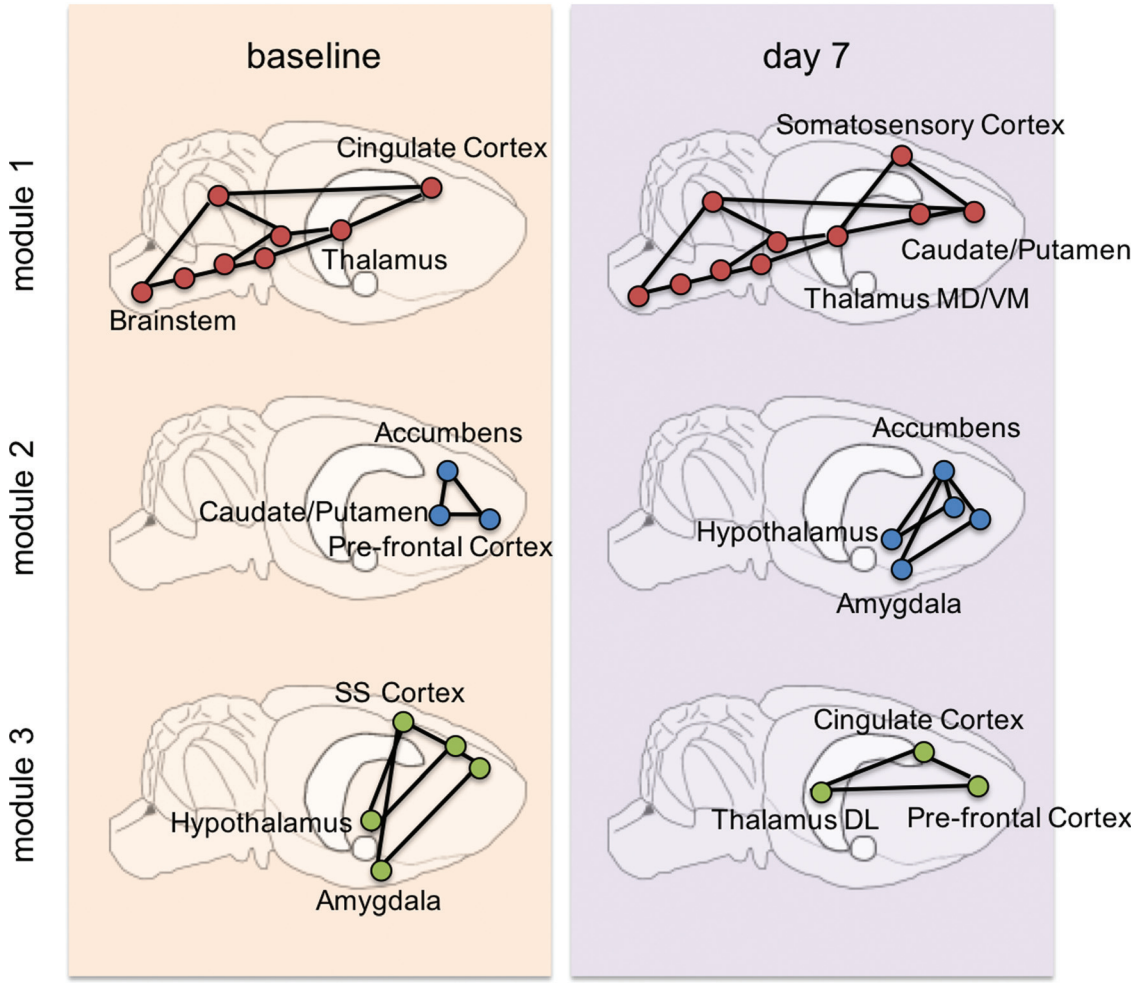

Fig. 6 The brain can be represented as a network: a collection of brain regions (nodes; circles) and connections between them (edges; lines). Applying this methodology to TMJ loading-induced pain, modifications in functional modules between baseline and after TMJ loading (day 7) are evident, as highlighted by changes in module-affiliation of brain regions.

increased brain activity in prefrontal-limbic regions in patients with knee OA that is not apparent in healthy controls [168]. In TMJ disorder, white matter alterations occur in the medullary dorsal horn of patients with pain for longer than 1 year [83], and differential brain activity is detectable in patients with painful TMJ disorder compared to controls [169]. Collectively, changes in brain activity and white matter connectivity suggest that persistent OA pain may alter *both* the structure and the function of the brain. However, since most of these changes have been studied in clinical populations, their time course and mechanisms are unknown.

Preliminary studies using a rat model of TMJ pain [13,170] suggest that modifications in functional brain connectivity occur within the first week corresponding to when joint pain develops. ^{18}F-FDG PET imaging of resting-state brains was collected at baseline before any stimulation and at day 7 (after 1 week of TMJ loading). Brain networks were constructed from PET scans to assess the topological relationships between brain regions. In order to characterize the presence and organization of functional domains, community detection techniques were used to identify *modules* [171–173] within the brain activity networks. At day 7, when pain is present [13], there is evidence of functional reorganization of brain regions in these modules (Fig. 6); there is also a transition from all regions of the thalamus clustering in module 1 (at baseline) to splitting these regions into modules 1 and 3 (at day 7) (Fig. 6). There is similar evidence for thalamic reorganization in TMJ pain in humans [82] and it is also implicated in neuropathic pain [166]. These findings also align with research in nonhuman primates that shows somatotopic reorganization of the ventral posterior thalamus in response to peripheral nerve injury [174]. Despite evidence for early thalamic changes in brain networks due to joint loading, additional work looking at brain network signatures in acute and chronic TMJ pain could help further elucidate possible supraspinal mechanisms that contribute to the maintenance of joint pain.

Summary

Facet joint and TMJ pain syndromes are complex disorders with mechanical, molecular, and nociceptive contributors. Despite some evidence of associations between these components, there is still a limited understanding of *how* mechanical forces that act on these joints and their tissues initiate and sustain pain. The development of in vitro systems that can specifically modulate isolated factors can be helpful in uncovering mechanisms relevant to the generation of joint pain. Such systems are particularly useful for evaluating combined effects of loading and molecular mediators on neuronal activation, such as degenerative enzymes and other potentially sensitizing molecules. However, such models must be combined with both in vivo and in silico approaches to develop

the most comprehensive understanding of pain. When translating findings into in vivo findings in animals and/or humans, different aspects of the pain experience can be measured. Combined measurement of evoked and spontaneous pain responses captures both the sensory, and potentially, the affective components of pain. Further, changes in CNS connectivity that are believed to maintain pain can be measured using functional imaging approaches. Functional brain imaging of in vivo models after joint loading and with treatment may clarify mechanisms of pain centralization. Overall, diagnostics are predicted to focus on imaging of active biological processes in painful joints, targeting critical molecular processes that mediate chronic pain.

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