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Diverse Role of Biological Plasticity in Low Back Pain and Its Impact on Sensorimotor Control of the Spine

Until recently, the search for biological mechanisms underlying chronic pain has focused primarily on nervous system dysfunction.[48] Increasingly, the contemporary view is that pain and injury involve a complex array of biological processes that engage multiple systems beyond simple changes in neural excitation, inhibition, and processing. The term *plasticity* is commonly ascribed to nervous system adaptation in pain, but can be expanded to *biological plasticity* to more broadly define the capacity of the array of biological processes to undergo change in the presence of pain and injury. These processes interact to shape the response of the individual, with potential for both negative and positive outcomes for the experience of pain, the health of tissues, and recovery.

This complexity has diverse implications for the presentation of sensorimotor changes, potential underlying mechanisms, and their relevance for long-term outcomes. This is particularly relevant for sensorimotor control of the spine, which refers to all the sensory and motor aspects of control of spine mechanics, from the brain to the muscle and other tissues. It is no longer sufficient to consider pain as simply the response to the discharge of nociceptive neurons. The contemporary understanding of pain involves consideration of different broad categories of pain with different underlying mechanisms, activation of a network of neural systems, neuroimmune interactions (peripherally and centrally), and tissue-level changes, as well as psychological and social domains. All of these have a potential role in the sensorimotor adaptation to pain, as well as in the development and maintenance of pain.

Together, this broadened understanding of the sensorimotor changes in pain and injury underpins the need to reconsider the role of sensorimotor control in the rehabilitation of back pain. The purpose of this commentary is to present a contemporary view of implications of the biology of pain and injury for sensorimotor function. The following section starts with a review of the contemporary understanding of the biology of pain

SYNOPSIS: Pain is complex. It is no longer acceptable to consider pain solely as a peripheral phenomenon involving activation of nociceptive neurons. The contemporary understanding of pain involves consideration of different underlying pain mechanisms and an increasing awareness of plasticity in all of the biological systems. Of note, recent advances in technology and understanding have highlighted the critical importance of neuroimmune interactions, both in the peripheral and central nervous systems, and the interaction between the nervous system and body tissues in the development and maintenance of pain, including low back pain (LBP). Further, the biology of many tissues changes when challenged by pain and injury, as reported in a growing body of literature on the biology of muscle, fat, and connective tissue. These advances in understanding of the complexity of LBP have implications for our understanding of pain and its interaction with the motor system, and may change how we consider motor control in the rehabilitation of LBP. This commentary provides a state-of-the-art overview of plasticity of biology in LBP. The paper is divided into 4 parts that address (1) biology of pain mechanisms, (2) neuroimmune interaction in the central nervous system, (3) neuroimmune interaction in the periphery, and (4) brain and peripheral tissue interaction. Each section considers the implications for clinical management of LBP.
J Orthop Sports Phys Ther 2019;49(6):389-401. doi:10.2519/jospt.2019.8716

KEY WORDS: *low back pain, lumbar spine, motor control, neuroimmune system, nociception, pain*

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mechanisms, and then considers biological processes that occur in the presence of pain and injury that impact the sensorimotor system at the brain, muscle/tissue, and in between.

Contemporary View of Biology of Pain

Pain is a unique, individual experience. Nevertheless, research has shed some light on its different underlying biological mechanisms, which vary from predominantly nociceptive to neuropathic, central sensitization, and mixed types of pain, each with a different relevance or relationship to sensorimotor control of the spine. *Nociceptive pain* (or perhaps more accurately, "pain associated with ongoing nociceptive input") is defined as pain that is experienced with actual or threatening damage to nonneural tissue and is driven primarily by activation of nociceptors.[92] Although direct evaluation of the activation of nociceptors is possible using microneurography,[136] it is generally not possible in clinical contexts, and the term *nociceptive pain* is often used when pain is considered to be proportional to expected nociceptive input[127] and is present within an otherwise normally functioning somatosensory system.[73,92] Such input may involve peripheral sensitization from the inflammatory system response, sometimes referred to as "inflammatory pain."[72] The term *nociceptive pain* directly contrasts with *neuropathic pain*,[92] which is defined as pain associated with a lesion or disease of the somatosensory nervous system.[92]

In many patients with pain, particularly those with more persistent symptoms, a clear origin for nociceptive input is lacking or is not severe enough to explain the pain experienced by the patient, and there is no evidence of damage or disease in the somatosensory system. In such patients, there is often clinical evidence of central (nervous system) sensitization,[118] which is a general term that encompasses many different processes (eg, activation, modulation, and modification of peripheral afferents or central neurons[145]) involving many different elements of the nervous system, from cells and synapses to whole networks. Although there is variation in the nervous system processes involved in central sensitization, this broad category of pain is defined as "an amplification of neural signaling within the central nervous system [CNS] that elicits pain hypersensitivity"[145] or "increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input."[92]

This is becoming recognized as a major mechanistic descriptor for chronic pain states.[73] Some specific terms have been proposed (eg, *nociplastic*, *algopathic*, and *nocipathic*).[73] The term *nociplastic* has been included in the taxonomy used by the International Association for the Study of Pain[60] to describe "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain." This term is not yet universally accepted and is argued by some to be too vague to be accepted as a replacement for other existing terms.[21,44] The term is used synonymously with the terms *central pain*,[41] *centralized pain*,[26] or *central sensitization pain*[103,126] (note that the term *central sensitization* refers to the neurophysiological process of sensitization, which may or may not contribute to this pain presentation, creating some confusion).

In the current clinical commentary, we use the term *nociplastic/central* to be inclusive of the related literature. In many patients, evidence of central sensitization is demonstrated by altered sensory processing in the brain,[130] with increased brain activity in areas known to be involved in acute pain sensations (insula, anterior cingulate cortex, and prefrontal cortex [PFC]), as well as regions not found to be active in response to noxious stimuli (various brain stem nuclei, dorsolateral frontal cortex, and parietal association cortex),[120] decreased activity in other regions, poor functioning of descending antinociceptive mechanisms,[147] and increased activity of brain-orchestrated nociceptive facilitatory pathways.[130] Psychological features (eg, catastrophization, fear of pain) are common and can moderate and/or mediate sensitization.[101] Many people with a clinical presentation of pain that is deemed "nociceptive" or "neuropathic" also often copresent with signs of central sensitization.[128]

A clinical approach, as outlined in the **TABLE**, has been proposed to classify people with pain into groups based on the clinical judgment of a predominant neuropathic, nociplastic/central, or nociceptive pain mechanism. This approach is based on research, including a Delphi study,[124] studies that compared clinical indicators of the 3 major pain types against clinical diagnosis,[125,126] and international expert opinion.[35,105] The test-retest reliability, interobserver reliability, concurrent validity, content validity, and prognostic value of the classification of patients based on presumed pain mechanism are unknown.

In addition to the 3 major mechanistic descriptors for chronic pain states, many patients also present with mixed types of pain, and there is some foundation to consider a group with predominant psychogenic pain.[103] Patients with this latter presentation may not fit within the other categories, but rather present with dominant maladaptive psychological features and illness behavior (eg, pain catastrophizing combined with pain hypervigilance, poor acceptance, depressive thoughts, and maladaptive pain coping styles such as avoidance behavior).

Pain Biology and Sensorimotor Control of the Spine The presentation and relevance of sensorimotor features of low back pain (LBP) may differ between the 3 different mechanisms of pain (nociceptive, neuropathic, and nociplastic/central) and likely have different relevance for management. For instance, motor control changes may be tightly related to nociceptive-type pain.[71] In that case, features of movement/posture and muscle activation may be responsible for

the suboptimal loading that maintains nociceptor discharge and its persistence beyond an acute injury. In neuropathic pain, symptoms can include features of particular relevance to sensorimotor control, such as motor weakness and sensory loss (including proprioception) driven by impaired propagation of action potentials along the nerve or ectopic potentials generated at the site of the lesion, both of which would lead to inaccurate information from the periphery being transmitted to the CNS. Further, muscle activation may be modified to unload or protect sensitized neural tissue.[9] In nociplastic/central pain, there can be diverse adaptations in sensorimotor function, which might be expressed as an excessive protection strategy that has little actual role in protecting tissues at risk,[57] reduced physical activity related to avoidance, or adaptation in the sensory representation of the body.[27,37] In each case, rehabilitation of sensorimotor control and exercise would have different targets.

A plausible hypothesis is that tailoring interventions to match patient presentations, including presumed underlying pain mechanisms, would improve outcomes, as has been described in detail elsewhere.[53] For those with ongoing nociceptor activity from tissue loading (ie, nociceptive pain), tailored treatment may involve optimization of loading through rehabilitation of motor control. For those with nociplastic/central pain, cognition-targeted exercise therapy combined with pain neuroscience education[85,104] to address pain cognitions and behaviors may be effective. This approach has been found to be superior to education on back and neck pain and general exercise in patients with chronic spinal pain.[84] Further, a recent randomized clinical trial showed that individuals with features of pain consistent with nociceptive pain (based on a questionnaire that identified patients with or without a relationship between pain and movement/postures) achieved greater clinical improvement with movement-based treatment (motor control training) than with behavioral therapy (graded activity).[83]

Neuroimmune Interactions in the Nervous System

Although neuronal mechanisms are likely to be fundamental for the genesis of chronic pain,[145] in the last decade animal studies have suggested that glial cells in the CNS (mainly microglia and astrocytes, and more recently also oligodendrocytes[47]) may play an important role in the development and/or maintenance of persistent pain conditions. In the presence of a pain-initiating event (eg, an injury), microglia and astrocytes transition to an "activated" state.[66,67] Glial activation refers to a series of cellular and molecular responses that include proliferation, morphological changes, increased or de novo expression of cell surface markers or receptors, and the production of cytokines and other inflammatory mediators.[68,108,112] In animal models of pain, activated glial cells upregulate the expression of receptors such as the adenosine triphosphate receptor $P2X_4$[138] and the chemokine receptor CX3CR1,[142] and increase the release of enzymes such as nitric oxide synthase[91] or inflammatory mediators

TABLE Clinical Approach to Classification of Individuals With Pain as Having Predominant Neuropathic, Nociplastic/Central, or Nociceptive Pain Mechanisms

Step	Description
1. Screen for neuropathic pain using the available international guidelines[35,137]	Classification of neuropathic pain would be concluded if 1. There is a history of relevant neurological lesion or disease 2. Pain distribution is neuroanatomically plausible 3. Supporting evidence is obtained by a clinical examination (eg, presence of negative sensory signs concordant with the lesion or disease of the somatosensory nervous system) 4. Objective diagnostic testing confirms the lesion or disease of the somatosensory nervous system • Neuropathic pain is defined as possible, probable, or definite based on satisfying criteria 1 to 2, 1 through 3, or 1 through 4, respectively • If criteria for neuropathic pain are not met, then move to step 2
2. Screen for nociceptive and central sensitization pain	Classification of pain predominantly related to nociceptor stimulation would be concluded if • Pain is localized to the areas of mechanical load, provoked by specific postures and movements, and has a predictable stimulus-response profile[127] • Pain experience is reasonably proportionate to the nature and extent of injury or pathology.[105] This might be gleaned from the extent of injury, pathology, and objective dysfunctions capable of generating nociceptive input (including imaging techniques and clinical examination) Classification of pain predominantly related to nociplastic/central sensitization mechanisms would be concluded if • Pain is somewhat variable/diffuse and does not follow a neuroanatomically logical pain pattern, defined as pain distribution that is not neuroanatomically plausible for the presumed source(s) of nociception.[105] Pain drawings can be used to standardize and optimize the assessment of the individual's pain distribution in a reliable and valid way.[86,87] Pain outside the area of presumed nociception is an established feature of central sensitization pain,[45,80] but is not diagnostic of nociplastic mechanisms (eg, pain outside neuroanatomical distribution can also present in neuropathic pain[90]) • Allodynia and/or hyperalgesia is identified outside the segmental area of primary nociception • Presence of unhealthy pain cognitions (eg, pain catastrophization) and behaviors (eg, activity avoidance), which mediate sensitization processes[141] • Classification can also be supported by identification of hypersensitivity of senses unrelated to the musculoskeletal system,[105] assessed using a tool such as the Central Sensitization Inventory.[89] Several studies support the clinimetric properties of the Central Sensitization Inventory in different countries[74,89,100]

such as the proinflammatory cytokines interleukin (IL)-1β, tumor necrosis factor (TNF), and IL-6,[66,146] and chemokines such as chemokine ligand-2.[24] These molecules sensitize neural pathways involved in pain[93] in a "pain produces pain" loop of central sensitization.

In animals, pain-related neuroinflammation is most commonly observed in the spinal cord[66] and sensory ganglia,[77] but more recently it was also discovered at the level of the brain, including in the rostral ventromedial medulla,[116,144] the trigeminal nuclear complex,[79,108] and the ventral posterolateral nucleus of the thalamus.[78,148] In the acute or subacute phase, glial activation can be considered as part of an adaptive response, as the development of temporary pain hypersensitivity can favor protection of the injured body part, limiting further tissue damage and promoting recovery. However, when glial activation is excessive, and/or does not promptly recede after the resolution of the initial insult, it can have deleterious effects and become the primary pathogenic element[111] mediating central sensitization. Importantly, drugs that reduce glial activation (eg, propentofylline or minocycline[94,131]) or that inhibit the action of glial products (eg, IL-1 receptor antagonists[143]) attenuate or inhibit protective responses to pain/nociception. Together, these observations indicate that glial activation represents neither a passive response to the pain-initiating event nor an epiphenomenon. Rather, neuroimmune activation has an active (and likely fundamental) role in the pathophysiology of persistent pain maintained by central sensitization.

Despite the rapidly growing animal literature supporting a role of glial cells in pain, the evidence of a role for glial activation in humans has been limited to a few post mortem immunohistochemical studies in the spinal cord of a handful of patients with complex regional pain syndrome[28] or human immunodeficiency virus–related neuropathic pain.[123] Recent work has provided early in vivo indications that glial cells may have a role in human LBP. Loggia et al[81] imaged the brains of individuals with chronic LBP, as well as those of pain-free healthy volunteers, using the recently developed positron emission tomography (PET) radioligand ^{11}C-PBR28.[17,19] The radioligand ^{11}C-PBR28 binds to the translocator protein (TSPO), which, within the CNS, is upregulated in activated microglia and reactive astrocytes in animal models of pain,[50,144] and is a putative imaging biomarker of inflammation.[22] Increased tracer binding in chronic LBP was observed most prominently in the thalamus, and with remarkable consistency across patients in the primary somatosensory and motor cortices (S1/M1) (**FIGURE 1**). Within the S1/M1, the PET signal increase was observed in the putative sensorimotor representations of the lumbar spine (in the postcentral gyrus[14]) and leg (in the paracentral lobule[82]). As almost all of these patients suffered from combined back and leg pain, the observed spatial pattern of PET signal increase suggests somatotopically organized glial activation in the S1/M1. This appears to mirror the body distribution of the patients' own pain symptoms[13] and has potential as a new mechanism to explain adaptation in spine sensorimotor function (see Neuroimmune Interactions in the Nervous System and Sensorimotor Control of the Spine below).

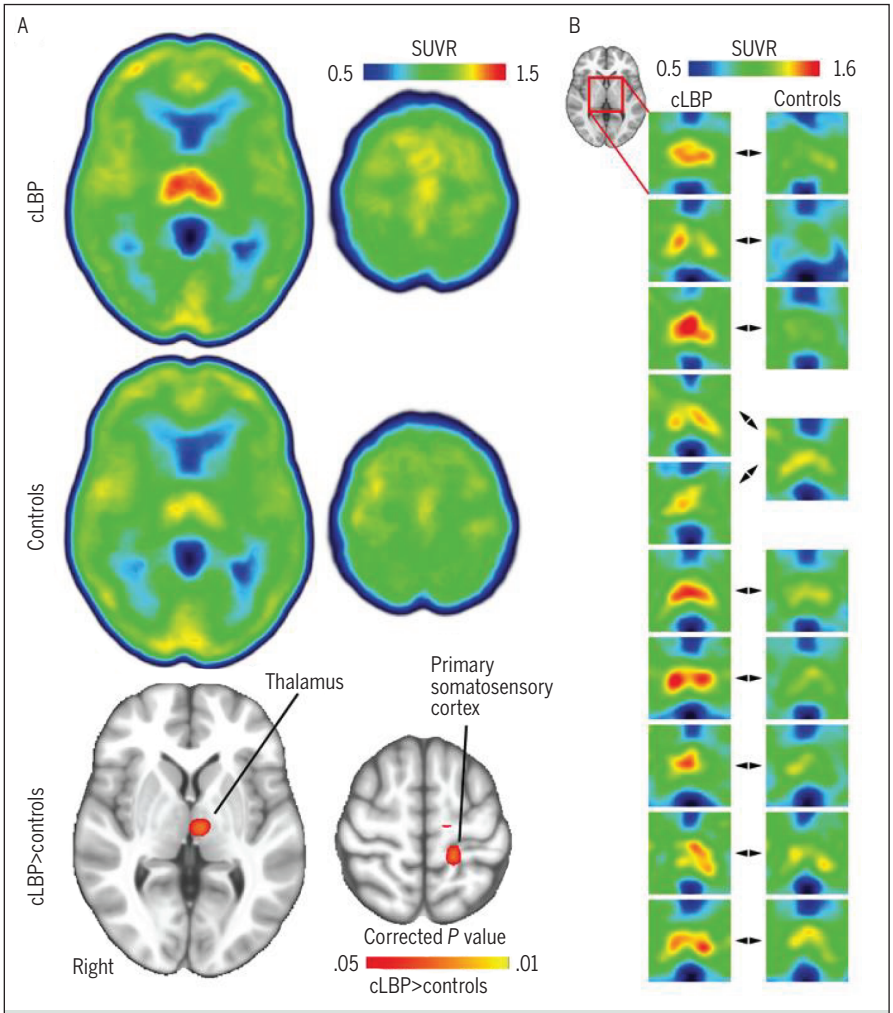

FIGURE 1. Evidence of glial activation in patients with cLBP. (A) Whole-brain group comparison; (B) individual data showing higher thalamic positron emission tomography signal in patients compared to sex-, age-, and binding affinity–matched controls. Abbreviations: cLBP, chronic low back pain; SUVR, standardized uptake value ratio. Adapted with permission from Loggia et al.[81]

More recently, using the same ^{11}C-PBR28 radioligand, Albrecht et al[3] observed increased TSPO signals in the spinal cord of humans with lumbar radiculopathy (an example of neuropathic pain), suggesting that glial activation could be observed at multiple sites in the CNS, as predicted by the preclinical literature. In the same study,[3] the authors also observed elevated TSPO signals at the level of the neuroforamina (containing the dorsal root ganglion and nerve roots) ipsilateral to the symptomatic leg. The amount of inflammation predicted the amount of perceived relief after epidural steroid injection. In this case, TSPO elevations are likely reflective of activation of peripheral immune cells, such as macrophages, but future studies need to provide experimental corroboration of this interpretation. Although these observations await future replication, they implicate glia in human pain disorders, supporting the exploration of glial cells as therapeutic targets for chronic pain disorders, from the perspectives of both modified processing of pain (nociplastic/central pain) and dysfunction related to sensorimotor control of the spine.

Of note, some clinical trials assessing therapeutic efficacy of pharmacological agents that modulate glial activity have reported negative results,[75] thus raising questions about the translatability and clinical relevance of animal work to the role of neuroimmune responses in human pain. On the other hand, humans suffering from subacute lumbar radiculopathy demonstrated a small but statistically significant improvement after a brief treatment with the tetracycline antibiotic minocycline,[140] which in animal models is a microglial inhibitor. The possibility of visualizing pain-related glial activation in vivo may help to identify patients most likely to benefit from glial modulators, as well as the optimal treatment duration or dosage. These studies may also allow us to evaluate whether glial activation explains sexual dimorphism in pain disorders, whereby different immune cells mediate pain hypersensitivity in different sexes, as recently suggested in animal studies.[129]

Neuroimmune Interactions in the Nervous System and Sensorimotor Control of the Spine In addition to the potential role of glial cells in the biology of pain, including several aspects of central sensitization,[115] these cells also influence function of related neurons. For instance, glial cells influence the availability of neurotransmitters,[34] remove unused synapses between neurons, are necessary for metabolic support of neurons,[52] and release molecules that regulate neuron structure, function, and connectivity.[43] Each of these mechanisms would influence the interaction between neurons and even the capacity to learn.[33,34] Thus, a plausible hypothesis is that the somatotopically localized change in glial activation (ie, affecting the specific motor regions of the brain that control the back muscles) might serve a role in modified motor and sensory function in persistent pain. Recent animal work highlights the involvement of glia in altered motor function in orofacial pain.[59] Glial cells might mediate the adaptation in sensorimotor function of trunk muscles or prevent recovery of sensorimotor control if their function impacts learning and adaptation. This is an exciting hypothesis, as it might provide a mechanism for sensorimotor changes in the CNS and offer new opportunities for therapy or treatments to combine with exercise. It is possible that glial activation might be more prevalent in the presence of neuropathic pain related to the back in humans, as has been reported for other body regions in animals,[59] which further highlights the need to consider pain mechanisms when planning treatment. For treatment, although anti-inflammatory pharmacological interventions could be predicted, an exciting possibility for future research is the possible role that exercise might have in moderation of glial activation, with the plausible potential to influence the regulation of neural processes underlying sensorimotor control of the spine. These proposals require direct investigation.

Neuroimmune Interaction in the Somatic Tissues

The purpose of immune responses in musculotendinous or other viscoelastic tissues is to phagocytose injured cells, such as cells with injured membranes and intracellular structures occurring as a consequence of overload, overstretch, compression, or anoxia. Injured cells release soluble factors, including potassium and hydrogen ions, adenosine triphosphate, and glutamate, that have been shown to reduce the intensity of stimulus needed for action-potential generation, leading to a state of relative nociceptor hypersensitivity by activating adjacent primary afferent terminals in animals,[5,10,113] among other possible mechanisms. Nearby mast cells activate, degranulate, and release histamine, bradykinin, inflammatory cytokines, and proteases. These substances further sensitize primary afferent terminals as well as increase vascular permeability (leading to infiltration of immune cells). Macrophages and cells that are injured, irritated, or apoptotic also produce inflammatory cytokines, molecules that are chemotactic for additional immune cell infiltration. These responses are hallmarks of acute inflammation, mediate peripheral sensitization, and are a typically short-lived and reversible event. However, if injury or initiating stimuli are repetitive or chronic, involved tissues have little chance to complete their healing processes and may develop persistent inflammation.[12] Chronic inflammation is characterized by the prolonged presence of large numbers of macrophages in and around tissues, which contribute to secondary tissue damage via prolonged phagocytic activity and release of cytotoxic free radicals. Inflammatory cytokines are also cytotoxic at high levels. Animal studies show that a vicious cycle of tissue injury and provocation of pain may occur.[12]

There are many consequences of increased tissue cytokines in animals. Most work relates to body regions other than the spine, but when data are available for the spine, we indicate it below. Various inflammatory cytokines (eg, IL-1α, IL-1β,

and TNF) can (1) induce synovial cells, lymphocytes, endothelial cells, and macrophages to produce more inflammatory cytokines and chemokines; (2) increase permeability of blood vessel walls and immune cell chemotaxis, as mentioned above; (3) promote fibrosis, as discussed further below; and (4) sensitize primary afferent terminals via their receptors, further enhancing pain[10,16,36] (**FIGURE 2**). Tumor necrosis factor signaling, for example, is important in the development of pain behaviors in animal models that can be prevented or reversed by early treatment with anti-inflammatory drugs in animals.[119] Such behaviors include cold allodynia, forepaw mechanical allodynia, muscle hyperalgesia, and declines in muscle strength.[1,8,31,61,70] Moreover, inflammatory cytokines can "spill over" from local tissues into the blood stream, circulate and potentially stimulate systemic inflammatory effects, and cause widespread secondary tissue damage and pain hypersensitivity.[10] Alternatively, systemic cytokines may be delivered to the local tissue.

Chronic overrelease of several cytokines can cause excessive fibroblast proliferation, including IL-1β and TNF, which are both proinflammatory and profibrogenic.[11] The M2-type macrophages are involved in wound repair and produce cytokines that aid tissue repair, including TGFβ1.[11,76] Animal studies show that overproduction of fibrogenic cytokines can lead to excessive activation of fibroblasts and collagen matrix deposition in a process called *tissue fibrosis*. Fibrosis in and around muscles, tendons, and nerves may distort dynamic biomechanical properties and increase tissue strain due to adherence to adjacent structures and subsequent reduction in dynamic tissue function.[30] For example, fibrosis in the connective tissue "container" surrounding nerves has been linked to chronic nerve compression,[15,106] known to increase pain behaviors in animals. Furthermore, collagen deposition can increase around individual myofibers or entire muscles and tendons, tethering structures to each other and to nerves within these structures—changes that can enhance pain behaviors[15,36] in addition to their potential role in modification of mechanics,[110] which has major relevance for sensorimotor control of the spine in LBP; however, research is required to assess translation of these findings to humans.

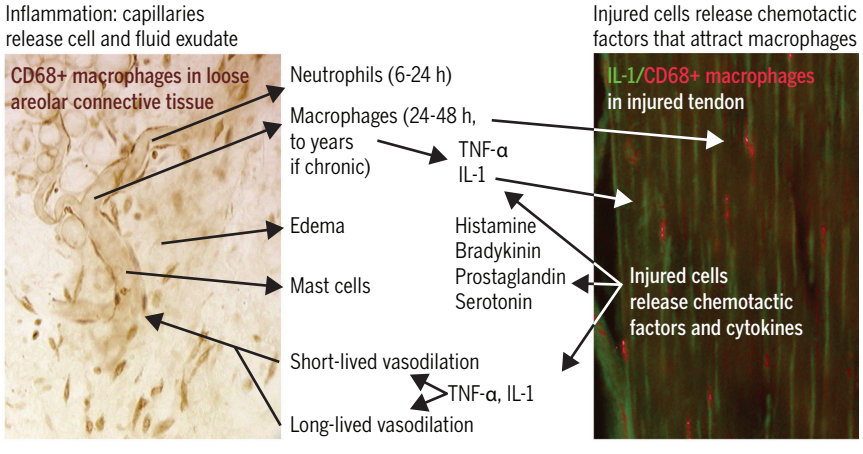

FIGURE 2. Sequence of events in acute inflammation in response to a mechanical injury stimulus. Mechanical injury can damage both vascular and musculoskeletal tissues and lead to the mobilization of neutrophils and macrophages by circulatory distribution and/or by chemotaxis induced by the presence of collagen fragments and chemokines at the injury site. Even when the vasculature is spared mechanical injury, the release of inflammatory mediators from tissue mast cells and injured cells causes vasodilation and leukocyte mobilization. Ideally, acute inflammation resolves and injured tissue heals, either completely or with the formation of a small fibrous scar. With a persistent injury stimulus, the inflammatory response itself may cause further injury and inflammation, thereby setting up a vicious cycle with subsequent incomplete healing and/or chronic inflammation. Abbreviations: IL, interleukin; TNF, tumor necrosis factor.

Substance P is an 11-amino acid neuropeptide involved in nociception peripherally and centrally.[49,65] Increased release of this neuropeptide peripherally plays a role in enhanced temperature hypersensitivity, mechanical hyperalgesia, and painful peripheral neuropathy in animals.[99,117,134,135,139] Interestingly, substance P is produced not only by neurons but also by peripheral immune cells (macrophages and mast cells), endothelial cells, fibroblasts, and tenocytes.[6,7,32,69] Increased levels of substance P can be stimulated by IL-1β, an increase that stimulates fibroblast proliferation and collagen production and remodeling.[7,25,38,69] There is also evidence that substance P is released from the central terminals of sensory axons, contributing to the central sensitization responses discussed earlier.[31,58,146] Thus, substance P production peripherally can be linked to peripheral immune responses, central sensitization, and enhanced pain behaviors in animals.

There is emerging evidence that changes in muscle do not depend on primary injury to the muscle. Muscle fatty infiltration, fibrosis, and structural changes (muscle atrophy, muscle fiber–type changes) are common in the back muscles, particularly the multifidus, in humans with LBP.[2,51,55] Although early changes may be mediated by neural changes such as reflex inhibition,[54] there is emerging evidence from animal studies to suggest that the later changes may be mediated by the inflammatory or peripheral substance P responses described above (**FIGURE 3**).[39] This was first identified in animals from ribonucleic acid analysis of muscle,[56] and more recent work has localized this increased proportion of M1 (proinflammatory) macrophages.[64] As the muscle is not injured in these animal models of intervertebral disc (IVD) injury, an important question is why the muscle enters a proinflammatory state. One possibility is that this is secondary to changes in the metabolic profile of muscle with the transition to a

greater proportion of fast (fatigable) muscle fibers.[64] Recent research in humans has identified similar processes in muscle in humans. Analysis of muscle samples harvested during surgery has identified a proinflammatory response similar to that observed in animals (James et al 2019, unpublished data).

Neuroimmune Interactions in Somatic Tissues and Sensorimotor Control of the Spine Peripheral immune system changes have potential relevance for sensorimotor control of the spine. First, sensitization of peripheral neurons will decrease the threshold for nociceptor discharge.[16] This may require greater control of tissue loading to prevent nociceptor discharge and may underlie increased muscle guarding. Second, the consequence of increased fibrosis and fatty changes has clear implications for tissue health in terms of the potential of muscle to control and move the spine as a result of muscle capacity (as the effector organ of the neural system) and tissue tethering from fibrosis, which will limit/distort movement. It is also plausible that modified tissue health impacts the quality of sensory information arising from the tissues.

This immune-mediated adaptation in the tissues points to potential benefit from addressing the immune response. Although pharmacological interventions may be obvious, other interventions are possible. Exercise can influence immune system activity, including macrophage activity in animals[42,63] and the associated accumulation of fibrosis.[62] Exercise may target the immune response in the tissues more effectively. This might underlie the efficacy of exercise for targeting sensorimotor control of the spine. There is preliminary evidence that muscle fatty replacement can be reversed with exercise in humans,[109] and tissue-level effects on fibrosis may require physical therapies (including manual therapy[15]) to address tissue mobility/health. Consideration of the time course of the condition and detailed assessments of muscle properties (eg, assessment of structural change with imaging), and perhaps systemic expression of cytokines, could guide treatment targeting.

Brain and Peripheral Tissue Interaction

Many anatomical components of the spine are linked to LBP, including IVDs, facet joints, muscles, and ligaments. Abnormalities in IVDs are observed in about 40% of clinical cases and are more prevalent in people with LBP,[18,107] implicating IVDs as a potential source of nociceptive input to maintain nociceptive pain in a subset of patients. However, there is a mismatch between IVD degeneration and LBP, and research has turned to a mouse model.

The secreted protein, acidic and rich in cysteine (SPARC)–null mouse model of progressive, age-dependent IVD degeneration suggests that increased disc innervation, loss of disc height, muscle inflammation,[63] sensory neuron plasticity, and neuroinflammation in the spinal cord can contribute to chronic LBP.[96-98] In addition, axial LBP (with likely nociceptive pain mechanisms) and nonaxial (ie, radicular, which is generally attributed to a neuropathic pain mechanism) LBP have different underlying mechanisms,[95] as outlined above, and respond differentially to both pharmacological and nonpharmacological treatments.[133] For example, axial discomfort is more sensitive to morphine than radicular pain in the same animals.[133] Given the different underlying pain mechanisms driving divergent symptoms (see Contemporary View of Biology of Pain section), using treatments that target the primary pathology or simultaneously targeting multiple pain mechanisms may improve patient outcomes. Interestingly, providing animals with access to running wheels for several months

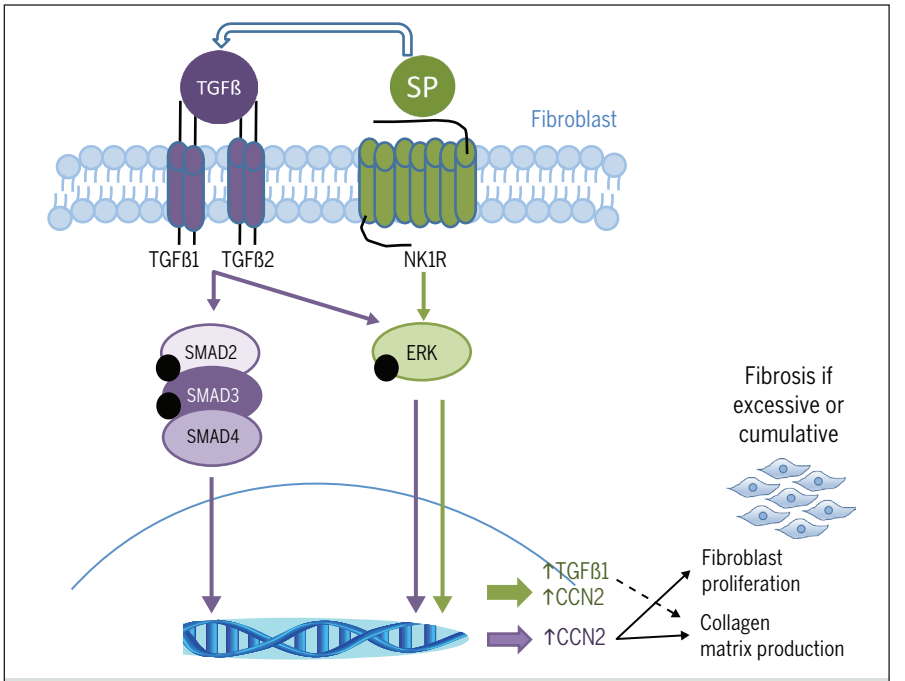

FIGURE 3. Mechanisms by which TGFβ1 and SP induce tissue fibrosis. On ligand binding and activation of TGFβ1 and TGFβ2 receptor complexes, SMAD2 and SMAD3 become phosphorylated (black circle). Phosphorylated SMAD2-phosphorylated SMAD3/SMAD4 complexes undergo nuclear translocation and then increased production of connective tissue growth factor (CCN2), a matricellular protein. The binding of TGFβ1 and the binding of SP to its main receptor, the NK1R, also leads to ERK phosphorylation (black circle), and then increased production and secretion of not only CCN2 but also additional TGFβ1. Both CCN2 and TGFβ1 stimulate fibroblast and tenocyte proliferation and collagen matrix production, the latter termed *fibrosis* if excessive or cumulative. Substance P is also a direct inducer of β1 production in primary cultured tenocytes.[39] Abbreviations: ERK, extracellular signal-regulated kinase; NK1R, neurokinin-1 receptor; SP, substance P; TGF, transforming growth factor.

attenuated both behavioral indices of pain and histological and biochemical signs of disc pathology, providing evidence for a relationship between pain and IVD degeneration (Millecamps et al, unpublished data). As outlined above (see Neuroimmune Interaction in the Somatic Tissues section), exercised animals also had reduced cytokine expression in muscle,[63,64] not only linking muscle changes with IVD and pain, but also highlighting a role of exercise in moderating this association.

In addition to peripheral structures, chronic pain is associated with long-term changes throughout the CNS that characterize central sensitization, as reviewed in detail in Brumagne et al[20] and considered in the preceding section. If peripheral structures such as IVDs contribute to chronic LBP and the brains of patients with chronic pain are different from those of pain-free controls, then a chicken-and-egg problem emerges: does living with chronic pain drive changes in the brain, or are individuals with less cortical gray matter, for example, predisposed to developing chronic pain? To address this, Seminowicz et al[121] performed a longitudinal study using a preclinical animal model of neuropathic pain following peripheral nerve injury. Adult rats underwent repeated anatomical brain magnetic resonance imaging prior to and over 20 weeks following induction of neuropathic pain. The frontal cortex of the neuropathic animals was smaller at the end of the study than in noninjured, sham-operated controls. Considering the observation that peripheral input can drive CNS pathology, it follows that the simultaneous targeting of peripheral factors would be important and may require concomitant consideration of CNS factors for pain management to be effective.

To investigate whether chronic pain-related differences in the CNS are permanent, patients with chronic LBP who were diagnosed with spinal structure–related pain and were scheduled for spine surgery or facet injections were recruited. Participants underwent structural and functional magnetic resonance imaging scans and completed questionnaires measuring pain and disability. Measures were repeated at 6 months. Findings were remarkable—both the LBP-associated reduction in the thickness of the PFC and altered functional activity returned toward control levels in individuals reporting improvements in pain or disability.[23,122] These studies not only suggested that peripheral input is associated with the initiation of supraspinal neuroplasticity, but also demonstrated that it might also maintain it. On the other hand, a recent trial showed that patients with chronic LBP responding well to conservative treatment did not change brain gray matter morphological features, even at 12-month follow-up.[84] Clinical improvements without detectable changes in brain gray matter morphological features suggest that further work is needed to clarify their relevance.

The mechanism underlying the pain-related changes in the PFC must be persistent, dynamically regulated, and reversible. *Epigenetic regulation*, a term used to describe reversible modifications to chromatin structure or genomic DNA that alter gene expression, is an ideal candidate to mediate between adverse exposure (eg, acute injury, progressive disc degeneration) and long-term neuroplastic changes that contribute to chronic pain. The importance of epigenetic modifications, such as DNA methylation, as a mechanism contributing to chronic pain is becoming increasingly clear.[29,40,102] By regulating which genes are and are not expressed in an individual cell, epigenetics allows the same genomic DNA to encode different types of cells and tissues in the same organism, such as brain cells and skin cells.[114]

That epigenetic mechanisms could mediate the long-term impact of injury and its potential reversibility through widespread reprogramming of gene expression in chronic pain, including in the PFC, is compelling. Preclinical data from studies of animal models of neuropathic pain (which is relevant for sciatic pain), but not yet back pain, provide support for this hypothesis, including the following: (1) chronic neuropathic pain is associated with altered global DNA methylation in the PFC,[132] (2) changes in the differential methylation of thousands of individual genes have been reported,[88] (3) dysregulation of the ribonucleic acid expression of hundreds of individual transcripts in the rodent PFC has been reported,[4] (4) changes in global DNA methylation in the PFC and pain sensitivity are both reversed by environmental enrichment,[132] (5) DNA methylation of individual functionally important genes in the PFC (eg, N-methyl-D-aspartate [NMDA] and opioid receptors) correlates with pain severity,[88] (6) treatment with an epigenetic drug attenuated behavioral signs of chronic pain,[46] and (7) analysis of peripheral T cells from animals with chronic neuropathic pain identified distinct patterns of differentially methylated genes.[88] Although the findings of these studies require validation in terms of their translation to humans, they provide the initial evidence for a plausible link between epigenetic programming and chronic neuropathic pain.

Brain and Peripheral Tissue Interaction and Sensorimotor Control of the Spine As highlighted in this section, debating whether chronic pain is a peripheral or a central phenomenon is no longer productive. In LBP, although degenerating IVDs have a role in some individuals and may contribute to input that maintains nociceptive pain, many other factors contribute. Peripheral nociceptive input mediated by suboptimal sensorimotor control of the spine can initiate and maintain maladaptive changes in brain structure and function. At the molecular level, epigenetic mechanisms are likely to mediate widespread changes in gene expression that contribute to brain pathology underlying central sensitization. Together, these observations provide a foundation for development of new treatments and treatment combinations. Combinations of pharmacological and nonpharmacological interventions

(eg, physical activity, manual therapy, environmental enrichment) that target both peripheral input from the spine and pathological CNS plasticity should be considered in the treatment of chronic LBP. Rehabilitation of LBP is likely to require a multifaceted approach that includes consideration of multiple interacting "bottom-up" and "top-down" biological mechanisms that interact with the neural processing of nociception and pain and sensorimotor control of the spine.

CONCLUSION

This commentary highlights the impact of biological processes on both the pain experience and sensorimotor control from the bottom up and top down. These processes not only impact the processing of nociception and pain, but also have a direct role in modification of neural processes associated with movement and sensation and the capacity of the muscles to control movement. Although it is plausible that targeted interventions will aid optimization of outcome, additional work is required to understand the underlying biological processes, the mutability of intervention, and the impact on the course of and recovery from LBP. ◉

ACKNOWLEDGMENTS: *The forum on which this body of research was based, "State-of-the-Art in Motor Control and Low Back Pain: International Clinical and Research Expert Forum," was supported by the National Health and Medical Research Council of Australia, in collaboration with the North American Spine Society. The forum was chaired by Dr Paul Hodges.*

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