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Focus Article

Reconnecting the Brain With the Rest of the Body in Musculoskeletal Pain Research

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Abstract: A challenge in understanding chronic musculoskeletal pain is that research is often siloed between neuroscience, physical therapy/rehabilitation, orthopedics, and rheumatology which focus respectively on 1) neurally mediated effects on pain processes, 2) behavior and muscle activity, 3) tissue structure, and 4) inflammatory processes. Although these disciplines individually study important aspects of pain, there is a need for more cross-disciplinary research that can bridge between them. Identifying the gaps in knowledge is important to understand the whole body, especially at the interfaces between the silos—between brain function and behavior, between behavior and tissue structure, between musculoskeletal and immune systems, and between peripheral tissues and the nervous system. Research on "mind and body" practices can bridge across these silos and encourage a "whole person" approach to better understand musculoskeletal pain by bringing together the brain and the rest of the body.

Perspective:* *Research on chronic musculoskeletal pain is limited by significant knowledge gaps. To be fully integrated, musculoskeletal pain research will need to bridge across tissues, anatomical areas, and body systems. Research on mind and body approaches encourages a "whole person" approach to better understand musculoskeletal pain.

Key words: *Musculoskeletal pain, chronic pain, muscle, connective tissue, mind and body practices.*

Over the past few decades, pain research has greatly strengthened our view of chronic pain as a "disease of the brain." However, as our knowledge about the role of the nervous system in chronic pain continues to expand, some disconnects are emerging between this knowledge and our understanding of peripheral tissue pathology, particularly for chronic musculoskeletal pain. This article will outline some important gaps that stand in the way of understanding chronic musculoskeletal pain, as well as areas where substantial knowledge exists but is "siloed" in different fields of medicine that need better integration.

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Pain and the Brain

Throughout most of the 20th century, musculoskeletal pain was mainly approached through the lens of orthopedics, focusing on specific structures such as joints or intervertebral discs. However, in the last 2 decades or so, there has been a shift in emphasis to the neuro-affective components of chronic musculoskeletal pain, including peripheral and central sensitization, reduced descending inhibition, and functional/structural alterations of cortical networks referred to as the "pain matrix."[3,10,56]

In parallel to this evolution in basic pain mechanisms, there has been a shift in our clinical approach to the management of patients with chronic musculoskeletal pain, from a "biomedical" to a "biopsychosocial" model.[23,34,45] There is indeed ample evidence that successfully treating musculoskeletal pain involves more than simply "fixing the broken part." This is exemplified in the field of low-back pain where diagnostic imaging of the spine is no longer recommended for the vast majority of patients[14] given the substantial portion of asymptomatic patients with demonstrable disc bulges or herniations,[19] along with poor correlations between radiological findings and symptoms of back pain.[17,70] This has caused the research pendulum to swing away from diagnosing structural causes of musculoskeletal pain and toward psychological factors, such as fear avoidance and depression in predicting how patients with chronic pain respond to treatment.[26] However, this shift toward the psychological elements of musculoskeletal pain may be neglecting some important sources of peripheral tissue nociception that we have yet to fully understand.[55] In the back, for example, there is evidence that important somatic "pain generators" may exist in tissues other than the spine (e.g., muscle, fasciae),[1,32] and integrative models are emerging that incorporate plasticity in these tissues as well as the nervous system into an integrated biopsychosocial whole.[27,31,39] A similar phenomenon is beginning to happen in the field of osteoarthritis. While earlier studies were focused first on cartilage, then turned to psychological factors, newer integrative models are increasingly incorporating extra-articular connective tissues and muscles as well.[15,44,76]

A more general question then might be: when a patient experiences musculoskeletal pain that lasts more than 3 months, is the pain "all in the brain" or could there be musculoskeletal tissue pathology that we do not yet fully understand phenotypically, but could contribute to pain chronicity? And if so, how would the musculoskeletal and neuro-affective components interact, and could understanding their interaction help develop better integrative treatment and prevention strategies?

Myofascial Tissues: Important Pieces of the Chronic Pain Puzzle

There is much interest in understanding mechanisms of "acute to chronic pain transition," most of them involving the nervous system and brain.[12] However, there is evidence that chronic inflammatory processes within soft tissues could play a role as well, especially with repeated trauma.[5] Small "soft tissue" injuries, such as sprains involving connective tissue and/or muscle are common and cause acute pain, inflammation, and muscle spasms that usually resolve within 48 to 72 hours but can progress to chronic pain.[59] In an animal model, rats who had to pull a lever repetitively for 3 to 6 weeks to get a reward developed chronic macrophage infiltration and fibrosis in tendons, muscles, and loose connective tissue.[5] Inflammation is important because it can sensitize deep fascia nociceptive neurons,[32] and cause tissue acidosis, which has been associated with musculoskeletal pain in several animal models.[1]

Even when pain and inflammation resolve, scarring and adhesions can cause movement restrictions that accumulate over time.[29] After an injury or in the presence of muscle disuse, perimuscular and intramuscular fibrosis is a main driver of muscle shortening, atrophy, and fatty infiltration, especially in the presence of inflammation.[49,57] In humans, cross-sectional studies have shown abnormalities of paraspinal muscles including atrophy, fibrosis, and fatty infiltration in patients with chronic low-back pain, compared with controls without back pain.[53,69,73] However, these measurements tend to be highly variable across subjects and have poor predictive value for future pain or disability.[53,61] One problem might be that these studies tend to focus on isolated muscles (e.g., multifidus, transversus abdominis), while the overall picture is undoubtedly more complex. For example, a patient with "tight" hamstrings, weak multifidi and chronic neck pain may have posture and alignment abnormalities that could underlie all three problems. The recent discovery that a substantial proportion of muscle forces are transmitted to neighboring structures via epimysium and fasciae, in addition to tendons, underscores the importance of understanding if and how muscle function becomes altered when adhesions form between adjacent fascia layers as a result of injury or chronic inflammation.[36,75] Although a full "personalized" phenotypic understanding of musculoskeletal pain for individual patients may not be realistic for some time, a better understanding of myofascial tissue will help to build biomechanical models across multiple body regions.

One particularly vexing aspect of muscle dysfunction that has eluded scientific understanding to date is the phenomenon of myofascial "trigger points." The clinical literature has for decades included descriptions of focal indurated and tender bands or "knots" commonly found within shortened or weak muscles.[20,66,71] Following unhabitual exercise or repetitive movement, these focal areas can become spontaneously painful and cause local and/or referred pain that typically resolves within a few days, but commonly recurs in a chronic pattern.[71] Remarkably, there has been a near complete lack of imaging methods or animal models to investigate the pathophysiological underpinnings of these clinical observations. This is beginning to change, however, as we are seeing the emergence of new magnetic resonance elastography methods, as well as a rodent model of myofascial trigger points combining a soft tissue injury with repeated bouts of exercise.[13,40] What role "myofascial" tissues play in chronic musculoskeletal back pain is clearly a substantial gap area in need of more research.[31]

Connecting Brain and Body Through Motor Behavior: Closing the Chronic Pain Loop

A biopsychosocial approach to chronic musculoskeletal pain needs to include not only its biological and psychosocial components, but also how these components influence one another. Motor behavior plays a pivotal role in musculoskeletal pain because body movements are both altered by pain and can feed forward to cause further deterioration of musculoskeletal tissues. There is considerable evidence from physical therapy research that patients with low-back pain have altered movement strategies that evolve over time.[31] A common pattern observed when back pain becomes chronic is increased rigidity of the trunk, increased resting electromyography activity, reduced trunk counter-rotation, and impaired sensorimotor control.[35,47] Fear avoidance contributes to the movement impairment, as people become afraid to move and adopt movement strategies that attempt to protect from further injury.[46] Fear avoidance can ultimately lead to withdrawal and social isolation, with increasing sedentary behavior and deconditioning.[42]

There is evidence that body movements influence muscle growth and regeneration[4] as well as connective tissue remodeling.[2,52,72] Importantly, the shape of our musculoskeletal tissues reflects the movements that we do, as well as those that we *do not* do, such that tissues becomes less mobile in the directions that are not moved habitually due to poor posture and/or sedentary lifestyle.[18,28,63,65] Sedentary behavior, poor posture, and joint misalignment also can contribute to muscle shortening, fibrosis, and dysfunction.[74] In a cross-sectional study, participants with chronic low-back pain of more than 12 months duration had on average less shear plane motion between adjacent thoracolumbar fascia layers compared with subjects without low-back pain.[38] Similar findings were seen in another study in pigs, in which a minor fascia injury and movement restriction had additive effects.[7] These findings suggest that a combination of reduced movement and inflammation can lead to adhesions between adjacent connective tissue layers, thus converting a functional restriction into a structural one. An important current gap in knowledge is whether the presence of fascia adhesions creates abnormal load distributions through tissues that put vulnerable structure such as joints and intervertebral discs at risk of premature degeneration. There is, in general, need for more research on the cumulative effects of motor behavior in everyday activities on the structure and function of musculoskeletal tissues over the lifespan.

Mind and Body Approaches to Chronic Musculoskeletal Pain

Given the enormous burden posed by disability due to chronic musculoskeletal pain, as well as the increasing sedentary behavior in contemporary society, it is imperative that we better understand mechanisms that may lead to the progression from soft tissue injury to inflammation, movement restriction, and further deterioration of tissue structure, posture, and movement. We also need more research to identify preventive strategies, such as changing or improving movements, to stop and potentially reverse such a vicious cycle.

Changing a movement pattern first and foremost requires awareness of the habitual movement or faulty posture.[51] Mind and body exercises and hands-on movement reeducation aim to bring awareness and correct faulty movement habits and offer a window of opportunity to prevent or reverse tissue abnormalities and reduce pain.[58] Rehabilitative exercises have had mixed success when focusing on strengthening specific muscles (e.g., stabilization exercises for patents with low-back pain).[25,41] On the other hand, less well-studied techniques and exercises that address whole body posture and movement could be useful in helping patients become aware of, and correct, posture and movement habits that may underlie seemingly "unrelated" musculoskeletal pain in different parts of the body.[30,50] Furthermore, techniques and practices that emphasize awareness training can help patients understand limiting behaviors (such as fear of movement), which can impair progress.[67]

Mind and body practices include a large and diverse group of procedures or techniques administered or taught by a trained practitioner or teacher. In general, these practices fall into 3 broad categories: 1) practices whose primary therapeutic input is mental, such as mindfulness-based meditation, cognitive-behavior therapy, hypnosis, and relaxation techniques; 2) body-based treatments such as massage, chiropractic, and acupuncture whose primary input is physical; and 3) practices such as yoga and tai chi whose input is both mind- and body-based. Although these practices fall into the area of "complementary" therapies, they are increasingly being integrated into conventional treatments such as clinical psychology and physical and exercise therapy.

A number of studies have shown that techniques with a mind-based component such as meditation, cognitive-behavior therapy, and yoga can enhance pain inhibition.[68,77] There is also some emerging research suggesting that some of these techniques have beneficial effects on areas of the brain related to emotional pain processing such as the insula, cingulate, and prefrontal cortex, which may include increasing gray matter volume and white matter integrity.[24,68] Mind-based therapies also reduce fear of movement and catastrophizing and improve functional behavior in patients with chronic pain.[11,67]

Important further questions are whether reducing fear of movement and changing movement patterns can measurably alter pathological processes with musculoskeletal tissues such as inflammation and fibrosis. Several studies in animal models have shown that massage and stretching can reduce connective tissue macrophage infiltration, collagen deposition, inflammation, and fibrosis.[8,9,16] There is also evidence that acupuncture needling mechanically engages connective tissue and may have local effects similar to manual therapies, as well as "deactivate" myofascial trigger points by eliciting a characteristic twitch response.[37,40,71] Additionally, the sensory input produced during acupuncture needling seems to have many neuro-affective effects in common with those of mind-based treatments, including descending pain inhibition and activation of pain matrix brain areas.[33] Mind and body therapies such as yoga and tai chi potentially combine all 3 types of beneficial effects: enhanced descending pain inhibition, behaviorally mediated improvement in movement patterns, and direct stretching of tissues.

An overarching challenge of investigating physical-based therapies, such as massage and spinal manipulation, as well as complex interventions, such as yoga and acupuncture, is that they are difficult to standardize across clinicians or treatment "style." Although this can be perceived as an obstacle to rigorous research, it also constitutes a healthy challenge that can motivate better study designs that will benefit research as a whole. It is also becoming increasingly clear that, especially for non-pharmacologic interventions, a "one-size-fits-all" approach to treatment is not optimal, and individualized approaches that treat each patient as a unique individual may be key to success.[21] Pragmatic clinical trial designs can test the effectiveness of individualized interventions, while preserving the ecological validity of the treatment.[64] This includes multimodal treatments delivered as a flexible "package" where the goal of the study is to compare the overall effect with a control intervention such a drug or other established "usual care" approach. While such studies cannot determine whether any given treatment component is responsible for an overall therapeutic effect, this can be tackled by other types of translational studies combining clinical and mechanistic endpoints. A promising approach is "interventional phenotyping," or classifying patients into phenotypic subgroups post hoc according to their clinical response to the overall treatment.[22] The increasing availability of wearable sensors to continuously record multiple physiological and even biochemical data over long time periods is also offering promising new possibilities to explore the effects of complex or multimodal treatments.[54] In such large multidimensional data sets, Explainable Artificial Intelligence can be used to identify differences in phenotypic patterns between subgroup of patients that either did, or did not, respond to a treatment.[43] These types of analyses can then generate mechanistic hypotheses that can be "reverse-translated" into animal/and or human studies.

Bridging Across Silos

Despite substantial progress in specific areas in the past decade, research on chronic musculoskeletal pain is limited by significant knowledge gaps. For example, chronic musculoskeletal pain research is often siloed

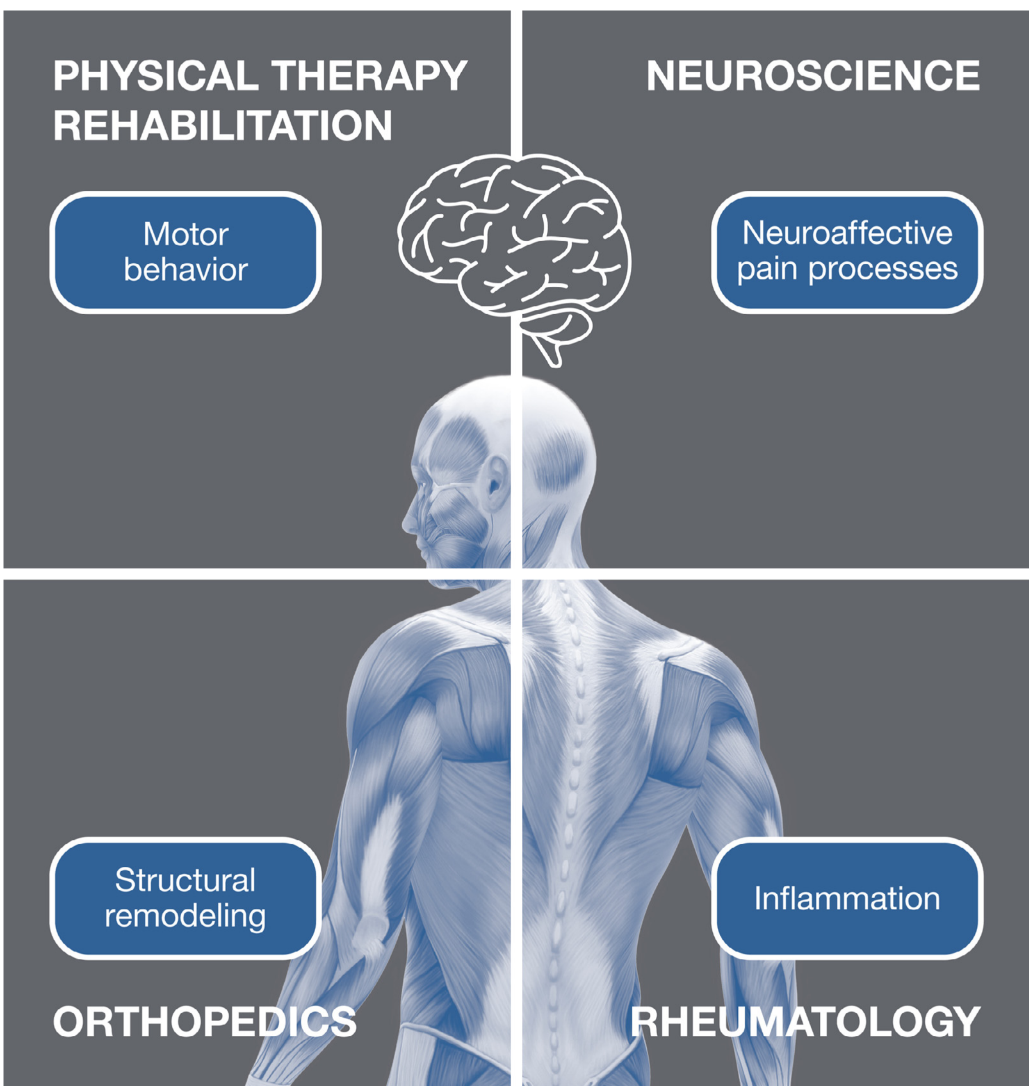

Figure 1. Integrative approach to musculoskeletal pain, bridging across neuroscience, physical therapy and rehabilitation, orthopedics, and rheumatology "silos."

between 1) neuroscience, which focuses on neutrally mediated effects on pain processes; 2) physical therapy and rehabilitation, which focus on behaviorally mediated effects on muscle activity; 3) orthopedics, which focuses on musculoskeletal tissue structure; and 4) rheumatology, which focuses on inflammatory processes within connective tissues (Fig 1). These are all important aspects of musculoskeletal pain, but there is a need for more cross-disciplinary research that can integrate these disciplines. Expanding this concept to other conditions that are often co-morbid with musculoskeletal pain, there is still much to learn about the connections between organ systems—such as between respiratory and gastrointestinal, between musculoskeletal and gastrointestinal or genitourinary systems—which can help us think about the whole body and advance our understanding of chronic pain related to conditions such as irritable bowel syndrome and interstitial cystitis.

Clearly, no single experiment or clinical study can address all these components at once, and integrating research across many disciplines poses substantial challenges. But identifying the gaps in knowledge is important to understand the whole body, especially at the interfaces between the silos—between brain function and behavior, between behavior and tissue structure, between musculoskeletal and immune systems, and between musculoskeletal tissues and the nervous system. Some interdisciplinary groups have been working at these interfaces with promising results. Physical therapy, which traditionally had focused on musculoskeletal function, is increasingly bridging to psychological behavior and neuroscience.[31] Several neuroscience groups have explored the sensory innervation of deep tissues, as well as the interactions between inflammation and mechanosensation.[48,62] Research on temporomandibular disorders is increasingly reaching across disciplines, as it is becoming clear that this problem involves musculoskeletal components beyond the temporomandibular joint itself, as well as psychological factors.[23] “Fascia” research is an emerging cross-cutting field bridging orthopedics, sports medicine, and rheumatology.[6,60,78]

An important additional challenge is that, even with more integrated research, musculoskeletal pain is often compartmentalized by body region (e.g., low back, knee, shoulder, temporomandibular area), such that common basic mechanisms relevant to musculoskeletal pain in general are difficult to synthesize. Another challenging aspect of musculoskeletal research is that specialized tissues and structures such as cartilage and intervertebral discs are often studied in isolation to the tissues anatomically connected to them. For example, studies of periarticular connective tissues often include synovium, ligaments, and joint capsules, but rarely the fasciae and aponeuroses that connect these structures to the rest of the limb or body region. Imaging of musculoskeletal structures reflects this emphasis, as much as musculoskeletal radiology focuses on bones and joints, and standard clinical MRI methods are not optimized to differentiate “soft” connective tissue from muscle or fat. Improved imaging methods, including dynamic soft tissue imaging, especially if combined with measures of muscle metabolism, can aid in this effort.

To be fully integrated, musculoskeletal pain research will need to bridge across tissues, anatomical areas, and body systems. Research on mind and body approaches is well situated by its very nature to encourage a “whole person” approach to better understand musculoskeletal pain, and this needs to begin by reconnecting the brain with the rest of the body.

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