Myofascial pain arises from muscle and its connective tissue. This noninflammatory condition is distinguished from other soft tissue disorders such as fibromyalgia, tendonitis, and bursitis. It presents with regional pain, often present in select quadrants of the body, and is accompanied by increased tension and decreased flexibility in the related muscle and fascia. Myofascial pain may present independently but is often a component of many acute and chronic pain conditions. Critical in its diagnosis is the presence of one or more myofascial trigger points (MTrPs)—discrete, hyperirritable nodules located in a taut band of skeletal muscle that are palpable during physical examination (Figure 1). Active MTrPs cause spontaneous pain in surrounding tissue and/or distant sites in particular referral patterns. Latent MTrPs have a similar physical finding, but are only painful upon deep palpation. Both active and latent MTrPs may cause muscle dysfunction, weakness, and a limited range of motion.

Unique Neurobiology of Muscle Pain
Muscle pain has a unique neurobiology with distinctive characteristics that are critical in explaining the clinical presentation of myofascial pain. Muscle pain can often be described as aching, cramping, deep, and difficult to localize. It is distinguished from cutaneous pain in that muscle pain involves nociceptive-specific neurons in the brainstem and spinal cord (1,2) and activates unique cortical areas that are associated with affective or emotional components of pain (3). Although muscle nociception is inhibited more intensely than cutaneous nociception by descending pain-modulating pathways (4,5), persistent muscle nociception is more effective at inducing maladaptive neuroplastic changes within the dorsal horn (6). Such neuroplastic changes support the clinical observation that muscle pain is often difficult to resolve.

Characteristics, Evaluation, and Diagnostic Criteria
An MTrP has been defined as a “hyperirritable spot, usually within a taut band of skeletal muscle or in the muscle’s fascia, that is painful on compression and that can give rise to characteristic referred pain, tenderness, and autonomic phenomena (7).” Accordingly, active MTrPs have a significantly lower pain pressure threshold than latent MTrPs and normal, uninvolved muscle tissue (8). Diagnosis depends exclusively upon history and physical examination, including specialized manual palpation techniques (7).

Whereas MTrPs are associated with local pain upon palpation, it is also common for myofascial pain to be experienced in seemingly unrelated areas. Continued pressure over an active MTrP should cause increased local pain and mimic the patient’s reported referral pain patterns. A latent MTrP, though not spontaneously painful, is usually tender and may also be associated with referred pain upon palpation.
A characteristic physical finding of the MTrP is the presence of a local twitch response (LTR), an involuntary, localized contraction of muscle fibers that is both transient and rapid and can be elicited by manual palpation. While controversy still exists over diagnostic criteria of an MTrP, Gerwin described the following features: 1) an exquisitely tender spot found in a taut band of muscle; 2) an LTR and/or referred pain to distant sites upon manual palpation or needling of the tender spot; 3) restricted range of motion; 4) reproduction of the patient’s pain complaint through pressure on an active MTrP; 5) regional muscle weakness; and 6) autonomic symptoms (9).

MTrPs are the most common, yet misdiagnosed and inadequately treated component of nonarticular musculoskeletal pain disorders. Clinicians tend to treat the symptoms of muscle pain (e.g., with medications) rather than the cause, which are usually MTrPs. Muscle pain is often given little consideration because there is neither consensus on the diagnosis nor any standardized objective measures to verify the presence of MTrPs. To date, accurate diagnosis of myofascial pain depends exclusively upon the palpation skills, clinical acumen, and experience of the examiner.

Peripheral to Central Sensitization
Active MTrPs are a source of ongoing peripheral nociception that may induce central sensitization. Muscle nociception is especially effective at inducing central sensitization (6). Continuous input from peripheral muscle nociceptors may lead to changes in function and connectivity of sensory dorsal horn neurons through central sensitization. Such activity increases the “afferent drive” (i.e., impulses per second bombarding dorsal horn neurons in the spinal cord).

MTrPs are Associated with Peripheral Abnormalities
While the pathophysiology of myofascial pain remains enigmatic, various studies have begun to elucidate its underlying properties. Our research team has sought to determine if there are objective biochemical differences among active MTrPs, latent MTrPs, and normal muscle tissue. To accomplish this, we developed a novel microdialysis needle (Figures 2A and 2B) with the same size, shape, and characteristics of an acupuncture needle. Use of this needle allows us to safely and quantitatively measure the local biochemical environment of muscle in vivo using continuous, real-time sampling (10-12).

We chose to investigate the levels of biochemical substances known to be associated with sensitization, pain, intercellular signaling, and inflammation (e.g., inflammatory mediators, neuropeptides, catecholamines, cytokines, etc.) that are released from and act on muscle, nerve, and connective tissue. Results from studies on the upper trapezius muscle indicate that active MTrPs have a unique biochemical milieu compared to latent MTrPs and muscle without palpable MTrPs. Subjects with neck pain secondary to an active MTrP had significantly elevated local levels of endogenous substance P (SP), calcitonin gene-related peptide (CGRP), bradykinin (BK), serotonin/5-hydroxytryptamin (5-HT), norepinephrine (NE), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) compared to carefully matched controls (10-12). Interestingly, compared to controls, subjects with active MTrPs in the upper trapezius also had elevated levels of these biochemicals in a remote, unaffected muscle (the gastrocnemius) (11,12).

Figures 2A and 2B.
may help to explain why active MTrPs, which are associated with high concentrations of the biochemicals known to cause both peripheral and central sensitization, are acutely painful, tender, and a source of referred pain. Our biochemical studies have helped to establish the clinical importance of palpating and identifying active MTrPs. They also suggest that myofascial pain is an objective entity in the spectrum of clinical pain states and may also explain why specific treatments are effective. For example, studies have found that an injection of the serotonin antagonist tropisetron was found to be more effective than lidocaine in relieving pain from MTrPs (13,14). Fittingly, our research indicates elevated local levels of 5-HT in individuals suffering from active MTrPs. CGRP, which was also found to be elevated in these individuals (10-12), has implications for activity within the neuromuscular junction. CGRP enhances the release of acetylcholine (ACh) from the motor endplate, decreases the effectiveness of acetylcholinesterase (15,16), and upregulates the ACh-receptors in the muscle. As ACh activity becomes more pronounced, the frequency of miniature endplate potentials increases as does the development of persistent focal muscle fiber contraction, a defining characteristic of the MTrP (17).

Various electromyography studies suggest that spontaneous electrical activity (SEA) has an important role within MTrPs in muscle pain and central sensitization. SEA is dysfunctional endplate potential of the extrafusal muscle fiber (18) that is characteristic of MTrPs (18,19). Damage to the cell membrane, as a result of mechanical trauma, may cause muscle damage (20) that begins a series of events to cause SEA. Ca\(^{2+}\) overload (21) and an increase in Na\(^{+}\) permeability, accompanied by a Na\(^{+}\) influx (22), induces depolarization at the motor endplate (23-25). While other ion channels may also be responsible, this process also results in ACh release at the MTrP (26). SEA is a combination of endplate noise and endplate spikes generated by increased spontaneous release of ACh (27,28). As such, SEA may play a significant role in pain. A study in humans showed that lower pain pressure thresholds at MTrPs were associated with higher amplitudes of the SEA; thus, the irritability of an MTrP was highly correlated with the prevalence of local SEA (29). Furthermore, the SEA represents a focal muscle fiber contraction, contributing to the formation of muscle tension (30) and the taut band associated with MTrPs (26,31).

**MTrPs and Abnormalities in the Dorsal Horn**

A barrage of nociceptive activity in the periphery (i.e., afferent drive) has the ability to induce maladaptive neuroplastic alterations in the dorsal horn of the spinal cord. Mechanisms involved in central sensitization include a lowered activation threshold for excitatory neurons, reorganization of spinal cord neurons, and new synaptic connections. Further, sustained input from an active MTrP may induce apoptosis of inhibitory neurons at the segmental levels affected by the peripheral noxious input, and such an action can sensitize dorsal horn neurons leading to allodynia, hyperalgesia, temporal summation of pain (32), and expanded pain patterns. A possible explanation for this phenomenon is increased synaptic efficiency through activation of previously silent (ineffective) synapses in the dorsal horn. These findings are hallmarks of central sensitization and, as one can imagine, their clinical consequences may be very distressing to patients suffering from chronic myofascial pain. Furthermore, fear of movement may follow resulting in muscle disuse, weakness, and dysfunction. Evidence suggests that patients with MPS have an abnormal stress response, as indicated by highly activated sympathetic and hypothalamus-pituitary adrenal (HPA) systems (33).

The concept of opening previously ineffective connections was demonstrated in a rat myositis model. Experimentally-induced inflammation unmasked receptive fields remote from the original receptive field, indicating that dorsal horn connectivity expanded beyond the original neurons involved in nociceptive transmission (34). In this study, nociceptive input resulting in central hyperexcitability helps to explain referred pain patterns common to myofascial pain. Central sensitization may facilitate additional responses from other receptive fields as a result of convergent somatic and visceral input at the dorsal horn (35) via wide dynamic range (WDR) neurons located in Lamina IV and Lamina V. These neurons are called “wide dynamic range” because they receive afferent input from multiple sources including skin, muscle, viscera, periosteum, and bone. In addition to Lamina I, muscle afferents preferentially activate Lamina V. This neuroanatomical fact explains how muscle nociception and pain can spread to alternate structures (e.g., viscera) and, vice versa, how nociceptive input from these alternate structures (e.g., viscera) can manifest as muscle pain.
Furthermore, afferent fibers have the ability to sprout new spinal terminals that broaden synaptic contacts at the dorsal horn and may also contribute to expanded pain receptive fields (36). This change in functional connectivity may occur within a few hours of the initial peripheral nociception, even before metabolic and genetic alterations occur in dorsal horn neurons (37). Although latent MTrPs are not associated with spontaneous pain, palpation may cause referred pain. According to Mense, “pain referral from a latent TrP is probably due to the fact that the latent TrP has only ineffective connections with the central nervous system and that these synapses are located on neurons that supply regions remote from the TrP (38).”

There is a biochemical basis to explain the development of peripheral and central sensitization in muscle pain. Continuous activation of muscle nociceptors leads to the co-release of L-glutamate and SP at the pre-synaptic terminals of the dorsal horn. In addition to activation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors by L-glutamate at the post-synaptic terminal, SP facilitates activation of previously dormant N-methyl-D-aspartate (NMDA) receptors. This leads to maximal opening of calcium-permeable ion channels, which hyperexcites nociceptive neurons and causes apoptosis of inhibitory interneurons (39). Consequently, a persistent noxious bombardment from the periphery can create long-lasting alterations in the central nervous system. Metabolic and gene induction changes, such as cyclooxygenase-2 (COX-2) induction in dorsal horn neurons, are maximal several hours after an initial noxious stimulation and bolster functional changes after peripheral tissue injury (40). In turn, central sensitization may enhance MTrP sensitivity, resulting in decreased mechanical pain threshold (41) and increased amplitude of SEA (42).

Higher Brain Centers Dynamically Modulate Muscle Pain

As aforementioned, persistent afferent input from active MTrPs preferentially activates and sensitizes WDR neurons in the dorsal horn. The stimuli then ascend the spinothalamic tract to reach higher brain centers. In addition to activating the thalamus, muscle afferent input preferentially activates the limbic system (i.e., the anterior cingulate gyrus, insula, and amygdala), which plays a critical role in modulating muscle pain and the emotional or affective component to persistent pain (3). Increased activity in the limbic system leads to greater fear, anxiety, and stress. Niddam and colleagues demonstrated increased limbic system activity in patients with upper trapezius myofascial pain syndrome (43).

There is a dynamic balance between supraspinal descending facilitation and inhibition. For example, the rostral ventral medulla (RVM) is a relay area between the periaqueductal gray (a structure located in the midbrain) and the spinal cord. The RVM contains a population of “on” cells and “off” cells which can either increase or decrease the level of pain, respectively, through projections that modulate activity in the dorsal horn. Following initial tissue injury, the “on” cells serve a useful and protective purpose designed to prevent further damage. Under ordinary circumstances, tissue healing would lead to a decrease in “on” cell activity and an increase in “off” cell activity. However, in chronic musculoskeletal pain conditions, there appears to be an overall shift to a decrease in inhibition, presumably due to an imbalance of “on” cell and “off” cell activity (44).

Muscle pain also impairs diffuse noxious inhibitory control (DNIC) (45). Disrupted descending inhibition in chronic musculoskeletal pain may lead to an increase in pain sensitivity of muscle tissue (46). Current data suggest
that MTrPs are not merely a peripheral phenomenon but rather, they activate and sensitize WDR neurons in the dorsal horn and higher brain centers and may, in turn, be dynamically modulated by these structures (38,43).

Dry Needling and the Local Twitch Response

Dry needling is an effective, non-pharmacological treatment of MTrPs that has approached acceptance as the “standard of practice” for deactivating active MTrPs. It may be performed using either a superficial or deep dry needling technique. Elicitation of one or more local twitch responses (LTRs) is a goal of dry needling and often benefits those with pain secondary to MTrPs. Though the mechanism of an LTR is unknown, studies suggest a biochemical component. Following the induction of a single LTR, our group found a dramatic change in the biochemical milieu of the upper trapezius muscle. Within minutes of the LTR, the initially elevated levels of SP and CGRP within the active MTrP drastically decreased to levels approaching that of normal uninvolved muscle tissue. The reduction of these biochemcials in the local muscle area may be due to a small, localized increase in blood flow and/or nociceptor and mechanistic changes associated with an augmented inflammatory response (10,12). Though not designed as a treatment intervention, dry needling may, in fact, activate the descending inhibitory pain system and cause local deactivation of the MTrP (47).

Limitations of Digital Palpation

Current diagnostic standards for myofascial pain rely on palpation for the presence of MTrPs in a taut band of skeletal muscle (7). However, proper diagnosis requires a highly skilled clinician, and some studies have found low inter-rater reliability among examiners in their attempts to identify MTrPs (48,49). Furthermore, digital palpation does not 1) provide an objective, reliable, and sensitive method of diagnosis and measurement of treatment efficacy; 2) provide quantitative comparisons of the tissue properties before and after treatment; 3) objectively differentiate among active MTrPs, latent MTrPs, and palpably normal tissue;

Vibration sonoelastography can be used to visualize MTrPs in muscle.

Figures 4A and 4B.

(A) Upper trapezius muscle with a palpable MTrP. A hypoechoic region and a well-defined focal decrease of color variance indicating a localized stiffer region are visible.

(B) Normal upper trapezius muscle. A myofascial trigger point is not palpable and the normal muscle appears isoechoic and has uniform color variance.
4) objectively discriminate between superficial and deep MTrPs; and 5) permit objective study of the natural history of MTrPs.

Visualization and Characterization of MTrPs
There is a need to develop objective, repeatable, and reliable diagnostic tests for evaluating MTrPs and determining treatment outcome measures. Such measures can be used to properly diagnose MTrPs, understand their natural progression, and overcome the subjectivity and limitations of digital palpation. Accordingly, our group has applied three types of ultrasound diagnostic imaging techniques—grayscale (2D ultrasound), vibration sonoelastography (Figure 3), and Doppler—to differentiate tissue characteristics of MTrPs in the upper trapezius muscle compared to surrounding soft tissue.

These office-based measures are readily available, portable, and inexpensive imaging modalities, suitable for use in a clinician’s office. We have demonstrated that ultrasound elastography can serve as an objective image-based measure of MTrPs. Using ultrasound, MTrPs can be imaged, appearing as focal hypoechoic (darker) areas with a heterogeneous echotexture. MTrPs also show reduced vibration amplitude on elastography, indicating a localized area of stiffer tissue compared to surrounding soft tissue (Figure 4) (8,50).

Our studies have also revealed that MTrPs have a unique vascular environment. Doppler ultrasound was able to show differences in the microcirculation in and around active MTrPs compared to latent MTrPs and normal tissue. For example, blood flow waveform characteristics can be used to differentiate active and latent MTrPs. Blood flow reversal in diastole was associated with active MTrPs, indicating a highly resistant vascular bed. This may be due to a blood vessel compression by a local muscle contracture (e.g., an MTrP) and/or biochemically-mediated vasoconstriction of the local blood vessels (50,51). Further analysis has also demonstrated that active MTrPs have a significantly larger surface area than latent MTrPs and normal sites (8).

Summary
Myofascial trigger points are a very common yet enigmatic component of non-articular musculoskeletal pain and dysfunction that have been long recognized in clinical practice. However, these hyperirritable nodules are also present in many asymptomatic individuals. This dichotomy requires that clinicians learn to distinguish active from latent MTrPs in order to accurately identify and treat a myofascial component of pain. There is a lack of concrete scientific knowledge concerning the pathophysiology and pathogenesis of myofascial pain. However, recent lines of scientific investigation (e.g. histological, neurophysiological, biochemical, and imaging studies) have demonstrated objective abnormalities that support the assertion that MTrPs are a complex form of neuromuscular dysfunction, involving skeletal muscle as well as peripheral and central sensitization. Without proper medical treatment, latent MTrPs may become active, and pain from active MTrPs may persist indefinitely as dorsal horn neurons and higher brain centers undergo neuroplastic changes as a result of chronic nociception. Development of proper treatment depends upon identifying and targeting the mechanisms of myofascial pathology by addressing the contributing and perpetuating factors that maintain this pain syndrome.

Future Directions
Our group is currently developing a model for the peripheral and central mechanisms involved in myofascial pain. Now that we have identified objective differences that distinguish active MTrPs from latent MTrPs and normal tissue, we plan to further study the nature of MTrPs and surrounding soft tissue over time. Although painful MTrPs activate muscle nociceptors that, upon sustained noxious stimulation, initiate peripheral and central sensitization, what is their etiology and pathophysiology? What is the mechanism by which the pain state begins, evolves, and persists? What are the levels of antiinflammatory substances, analgesic substances, and muscle metabolites in the local biochemical milieu of muscle with and without MTrPs? How does a tender nodule progress to a myofascial pain syndrome? Which soft tissues are involved? Are there objective measures for assessing therapeutic outcomes? Future clinical research studies should focus on identifying the mechanisms responsible for the pathogenesis and pathophysiology of myofascial pain and linking the symptoms and physical findings to the physical properties and biochemical changes in the muscle tissue.
chronic pain and myofascial pain and teaches workshops on examination and treatment techniques including acupuncture and dry needling. His research has been published in the Journal of Applied Physiology, Archives of Physical Medicine and Rehabilitation, the Journal of Ultrasound in Medicine, and the Journal of Bodywork and Movement Therapies. Dr. Shah completed a Bravewell fellowship at the Arizona Center for Integrative Medicine and was selected by the American Academy of Pain Management as the 2010 recipient of the Janet Travell Clinical Pain Management Award.

Contributions to the article also made by Juliana Heimur, BA.

JULIANA HEIMUR received a B.A. from The George Washington University. She is a research assistant within the Rehabilitation Medicine Department at the National Institutes of Health in Bethesda, MD.

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