Neuroimaging of Muscle Pain in Humans

David M. Niddam[1,2], Jen-Chuen Hsieh[1,2,3,4]*

[1]*Laboratory of Integrated Brain Research, Taipei Veterans General Hospital, and* [2]*Brain Research Center,* [3]*Institute of Brain Science, and* [4]*Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.*

Neuroimaging has provided important information on how acute and chronic pain is processed in the human brain. The pain experience is now known to be the final product of activity in distributed networks consisting of multiple cortical and subcortical areas. Due to the complex nature of the pain experience, a single cerebral representation of pain does not exist. Instead, pain depends on the context in which it is experienced and is generated through variable expression of the different aspects of pain in conjunction with modulatory influences. While considerable data have been generated about the supraspinal organization of cutaneous pain, little is known about how nociceptive information from musculoskeletal tissue is processed in the brain. This is in spite of the fact that pain from musculoskeletal tissue is more frequently encountered in clinical practice, poses a bigger diagnostic problem and is insufficiently treated. Differences are known to exist between acute pain from cutaneous and muscular tissue in both psychophysical responses as well as in physiological characteristics. The 2 tissue types also differ in pain sensitivity to the same stimuli and in their response to analgesic substances. In this review, characteristics of acute and chronic muscle pain will be presented together with a brief overview of the methods of induction and psychophysical assessment of muscle pain. Results from the neuroimaging literature concerned with phasic and tonic muscle pain will be reviewed. [*J Chin Med Assoc* 2009;72(6):285–293]

Key Words: cerebral cortex, fMRI, muscle, pain, PET

Introduction

Since the beginning of the last decade, numerous studies have explored the brain mechanisms of both acute and chronic pain. Advances in noninvasive brain imaging combined with novel methods to induce pain have provided the substrate for this rapidly growing field of research. It is now well accepted that the pain experience is the final product of activity in distributed networks consisting of multiple cortical and subcortical areas. Brain regions contributing to processing of the different aspects (sensory/discriminative, affective/motivational, cognitive/attentive, motor) of the pain experience as well as to allodynia and hyperalgesia have been mapped in humans. However, due to the complex nature of the pain experience, a single cerebral representation of pain does not exist. Instead, pain depends on the context in which it is experienced and is generated through variable expression of the different aspects of pain in conjunction with modulatory influences.

While considerable data have been generated about the supraspinal organization of cutaneous pain, little is known about how nociceptive information from musculoskeletal tissue is processed in the brain. This is in spite of the fact that pain from musculoskeletal tissue is much more frequently encountered in clinical practice. Further, treatment of pain from deep tissue poses a bigger challenge than superficial cutaneous pain. The existing treatments are often insufficient and the extent to which patients are affected is much more severe.[1]

This review outlines the current knowledge on brain mechanisms of muscle pain in humans and how it differs from cutaneous pain processing. A short overview is provided of the physiology of muscular nociception and clinical muscle pain. The methods of induction and psychophysical assessment of experimental human muscle pain are then considered. These sections form the essential prerequisites for understanding brain imaging studies on human muscle pain. In this review, only studies based on functional magnetic resonance

*Correspondence to: Dr Jen-Chuen Hsieh, Brain Research Center, National Yang-Ming University, 155, Section 2, Li-Nong Street, Taipei, Taiwan, R.O.C.
E-mail: jchsieh@ym.edu.tw • Received: November 5, 2008 • Accepted: May 7, 2009

imaging (fMRI) and cerebral blood flow positron emission tomography (PET) will be discussed.

Characteristics of Acute and Chronic Muscle Pain

Acute muscle pain

Acute muscle pain is characterized by activation of muscle nociceptors in the periphery under normal conditions and results in a sensation of pain that is closely related to the duration of the noxious stimulus. Differences are known to exist between acute pain from cutaneous and muscular tissue systems in both psychophysical responses as well as in physiological characteristics. This is for example clear when comparing sensory manifestations. Pain from muscles is perceived as diffuse, nagging and cramp-like and is often also referred to other somatic structures distant from the site of origin. In contrast, cutaneous pain is perceived as sharp and burning and is well localized. Also, cutaneous pain is rarely referred to other sites.[2] The 2 tissue systems may also differ in pain sensitivity to the same stimuli and in their response to analgesic substances.[2,3] These differences can partially be explained by different peripheral and spinal mechanisms such as fiber and sensory receptor distribution and spinal projection sites.

Chronic muscle pain

The transition from acute to chronic pain involves functional and morphologic changes in the peripheral and central nervous system and is accompanied by release of sensitizing agents. Chronic muscle pain may develop from tissue damage provoked by, for example, trauma, ischemic contractions or inflammation. It is characterized by spontaneous ongoing pain, lowered pain threshold turning non-nociceptive input into pain (allodynia), and enhanced pain sensitivity (hyperalgesia). However, chronic muscle pain conditions are often also associated with evolving motor dysfunction such as muscle stiffness, muscle weakness, and restricted range of motion.[4]

Chronic muscle pain conditions frequently seen in the clinic include myofascial pain syndrome, tension type headache, low back pain, and temporomandibular disorder. These conditions are accompanied by structural changes in the muscle often leading to the formation of focal allodynic/hyperalgesic contractures termed *myofascial trigger points* (MTPs) (Figure 1). MTPs are thought to arise from trauma, overload or strain resulting in local ischemia and increased metabolism.[4] However, the exact pathophysiologic mechanism remains a matter of debate. Since acute and chronic stress often result in increased muscle tone, stress may not only serve as an initiating cause but also as a pain exacerbating factor.[5] Pain from MTPs is often also referred to distant regions, albeit in characteristic patterns. Since MTPs can remain undetected, pain referral can be a cause of confusion in diagnosis.[4]

Peripheral and central mechanisms

Muscle nociceptors are un-encapsulated "free" nerve endings formed by thin myelinated (group III/Aδ) and unmyelinated (group IV/C) afferent fibers. A large proportion of these fibers are polymodal, responding

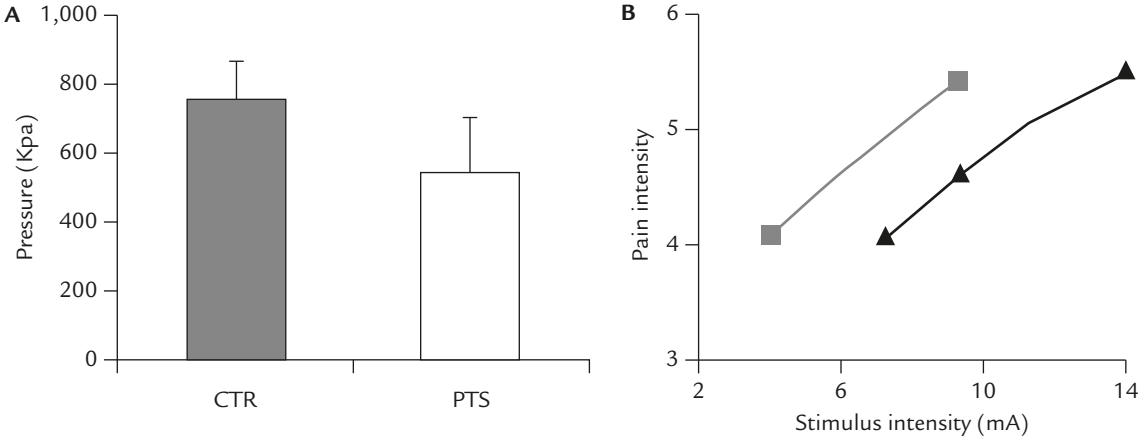

Figure 1. Hyperalgesia in patients with myofascial pain syndrome is demonstrated by: (A) lower pressure pain threshold; and (B) a leftward shift in stimulus-response function for intramuscular electrostimulation. Stimuli are applied to a myofascial trigger point in the upper trapezius muscle in patients (PTS, squares) and in an equivalent site in healthy controls (CTR, triangles). Modified with permission from Reference 18.

to chemical, mechanical and thermal stimulation.[6] Overall, the majority of sensory fibers from muscle nerves consist of unmyelinated afferent fibers.[7] Pulses from muscle nociceptors are transmitted past the sensory nerve bodies in the dorsal root ganglion into the spinal cord where they are integrated and modulated by interneurons before being transmitted to brain centers or onto reflex pathways. Some differences exist at the spinal cord level between nociceptive input from superficial and deep tissue. Projections from cutaneous nociceptors mainly terminate in lamina I and II in the spinal cord and projections from muscle nociceptors mainly terminate in lamina I and V. [8–12] Also, nociceptive input from superficial and deep tissue is known to influence spinal reflex pathways differently.[13–15]

Muscle nociceptors can be sensitized by muscle lesions, resulting in hyperexcitability of the receptors and spontaneous resting activity (peripheral sensitization). Prolonged input from muscle nociceptors leads to hyperexcitability of spinal neurons (central sensitization). In clinical muscle pain, peripheral and central sensitization acts together to induce spontaneous pain, allodynia, hyperalgesia, and referred pain. With further pain chronification, complex changes occur that may include extrasegmental expansion of receptive fields, synthesis of ion channel proteins, sprouting of spinal terminals of afferent fibers, formation of new synaptic contacts, and altered balance in descending influences. Once developed, central sensitization becomes independent of input from the lesioned muscle.

Induction of Experimental Muscle Pain

Several methods exist to experimentally induce muscle pain. These methods can be endogenous (ischemia or exercise) or exogenous (electrical, mechanical or chemical) and may result in phasic and/or tonic pain sensations.[16,17] Phasic muscle pain can be evoked by pressure to the muscle and electrical stimulation applied within the muscle or directly to the muscle afferents.[18–21] Tonic muscle pain can be evoked by pressure to the muscle, by ischemia and exercise, via fast repetitive electrical stimuli (~20 Hz), as well as by injection of chemical substances such as hypertonic saline (5%), capsaicin, bradykinin, and glutamate.[2,22–24] Electrical stimulation and hypertonic saline have been used in conjunction with fMRI and PET in several muscle pain studies.

Electrical stimulation is a nonspecific method that activates the nerve fiber directly. At low stimulus intensities, electrical stimulation activates the large nerve fibers. At increasing intensities, nerve fibers of decreasing diameter are activated. Consequently, at the high intensities needed to evoke pain, additional responses from a wide range of fibers, other than the smaller nociceptive fibers, will also be evoked. In addition, muscle twitches and possible limb movement will accompany the stimulation.

When applied within the muscle, hypertonic saline induces long-lasting cramp-like diffuse pain that closely mimics the chronic pain observed in patients. Apart from pain in the primary region, sensory manifestations such as referred pain, superficial mechanical hyperesthesia and autonomic reactions also occur.[22,25] The exact receptor transduction mechanism for hypertonic saline remains unknown. However, it is known to excite group III and IV afferent fibers and within the latter group, both low- and high-threshold mechanosensitive units are excited.[17] On the one hand, electrical stimuli allow for precise control of many stimulus parameters. On the other hand, it can be argued that since electrical stimuli do not constitute an adequate stimulus for the tissue, other methods such as injection of algogenic substances would be more closely related to clinical pain.

Psychophysical Assessment

In human pain research, psychophysics is considered an important tool for assessment of the multidimensional subjective pain experience. Within brain imaging, it provides an additional powerful tool for functional characterization of specific brain regions through correlational approaches. Psychophysical methods commonly applied in this field of research include visual analog scales, discrete numerical rating scales, verbal descriptor scales, and pain questionnaires. Scales can be used to quantify sensory attributes of a stimulus or a state. However, some scales are limited by not having all the properties of the number system.

Of the multiple pain dimensions and aspects, pain intensity and pain unpleasantness have predominantly been assessed. Pain intensity is characterized by words such as mild, moderate and strong and is considered part of the sensory-discriminative dimension of pain, which also encompasses other characteristics such as quality, duration and location. Pain unpleasantness is considered part of the affective dimension of pain and is characterized by words such as annoying, distressing and uncomfortable. The 2 pain dimensions are closely related to each other and the scores on a numeric rating scale are typically highly correlated. However, unpleasantness is not unique to the pain experience. In fact, it has been shown that separate manipulation of the 2 pain dimensions is possible.[26]

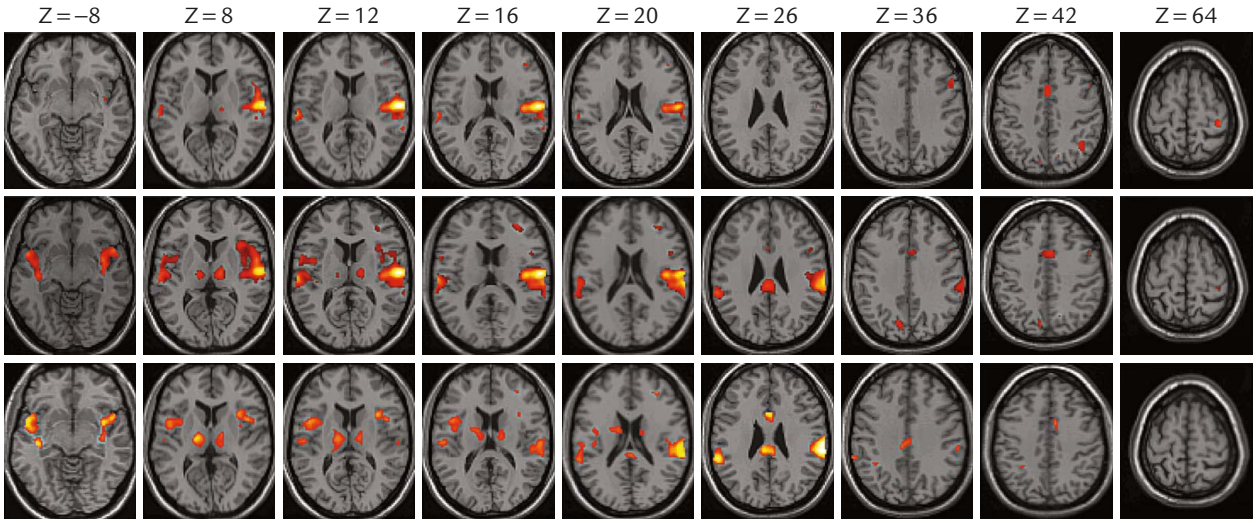

Figure 2. Blood oxygenation level dependent functional magnetic resonance imaging shows responses to non-painful intramuscular electrostimulation (IMES; top row), painful IMES (middle row) and painful – non-painful IMES (bottom row). The Z-coordinate denotes the axial section in the superior-inferior position relative to the commissural line (given in millimeters; positive = superior). Reproduced with permission from Reference 40.

Classical psychophysical methods can be used to measure pain thresholds, pain tolerance and stimulus-response functions. Threshold values can be determined by the *Method of Constant Stimuli*, the *Method of Limits*, or the *Method of Adjustment*. The most frequently used technique for determining pain thresholds is the *Method of Limits* in which the stimulus intensity is manipulated in either ascending or descending series.

Functional Imaging of Brain Hemodynamics

Hemodynamic imaging techniques are based on the principle that regional cerebral blood flow (rCBF) is redistributed to regions with neuronal activation. Regional increase in rCBF is closely related to an increase in the concentration of oxygenated blood. By injection of radioactive oxygen-15 labeled water ($H_2{}^{15}O$), PET can measure changes in rCBF directly. fMRI is typically based on the blood oxygenation level dependent (BOLD) technique. Both $H_2{}^{15}O$-PET and BOLD fMRI have been used extensively to explore the cerebral processing of cutaneous pain. Phasic stimuli are by far the most commonly applied type of stimuli used to induce acute cutaneous pain in imaging studies. The brain regions that most consistently respond include the thalamus, primary and secondary somatosensory areas (SI and SII), inferior parietal lobule (IPL), posterior, middle and anterior portions of insular and cingulate cortices, and medial and lateral prefrontal cortices (Figure 2).[27,28] Other less frequently observed brain regions include the cerebellum, basal ganglia and supplementary motor area (SMA). Patterns of functional activity are often interpreted as contributing to the generation of a specific aspect of the pain experience. Activation of the lateral portion of the thalamus, SI, SII, IPL, and posterior insula are mainly associated with the sensory-discriminative component of pain which include encoding of stimulus properties (intensity, localization, duration, and spatial and temporal discrimination). The medial portion of the thalamus, anterior insula and anterior cingulate cortex (ACC) are thought to subserve affective-motivational processing, and the prefrontal regions are thought to be involved in top-down modulatory processing including planning and cognitive mechanisms. Finally, the cerebellum, basal ganglia, SMA, and cingulate motor area (CMA) possibly subserve motor-related behavior such as planning and execution of motor-defensive strategies. Since specific brain regions may participate in the processing of several different aspects of the pain experience, the division into pain components may be regarded as too simplistic. Nonetheless, this approach does provide a useful framework to guide functional interpretations.

Tonic muscle pain and rCBF PET

Only a limited number of imaging studies have investigated pain originating from the muscle. Of these, the majority has been concerned with tonic pain induced by intramuscular injection of hypertonic saline. Other studies have used intramuscular electrostimulation (IMES) to induce tonic or phasic pain. The first brain imaging study investigating pain from muscles used

rCBF PET to compare tonic muscle pain, induced by high-frequency (20 Hz) IMES, with cutaneous pain, induced by phasic laser stimuli delivered to the skin above the same muscle.[29] Muscle pain resulted in increased rCBF in SII/posterior insula, IPL, posterior mid-cingulate (ACC/BA 24), and cerebellum. These areas completely overlapped with regions engaged by cutaneous pain. Thus, the authors concluded that a similar set of brain regions mediate muscle and cutaneous pain.

More recently, Korotkov and colleagues induced tonic pain by infusion of hypertonic saline and found pain-related increased rCBF in the mid insula, putamen and superior temporal gyrus (STG) and decreased activity in the IPL and middle frontal gyrus (BA9/10).[30] In another study from the same group employing similar methodology, activity associated with different phases (pre pain, early pain, late pain, post pain) of the tonic pain profile was explored.[31] Compared with the other conditions, increased activity was consistently observed for the early acute pain phase in the mid-posterior insula and STG. Increased pain-related activity was also observed in the putamen and inferior frontal gyrus when the early phase was compared to the later phases. Decreased IPL activity was only observed when the early phase was compared to the pre-pain baseline. Also, decreased anterior mid-cingulate (ACC/BA 24 and 32) activity was observed in the late pain phase compared to initial pain or baseline. Although pain from hypertonic saline is salient and unpleasant, these results surprisingly did not involve persistent increases in the limbic regions typically found in pain processing.

Kupers et al[32] employed methodology similar to that in the studies of Korotkov et al[30] and Thunberg et al[31] (hypertonic saline and rCBF PET) but found different results. Changes in activity during muscle pain were observed in a wide range of regions, some of which differed from those responding to non-painful cutaneous mechanical stimuli. Increased pain-specific activity was found in the cerebellum, anterior insula, posterior mid-cingulate (caudal CMA/BA 24), and perigenual cingulate (ACC/BA 32). Decreased responses were found in the amygdala and subgenual cingulate (ACC/BA 25). Nonspecific loci shared between pain and mechanical stimuli included the posterior insula, IPL, dorsolateral prefrontal cortex, anterior mid-cingulate (ACC/BA 32), and the brain stem. A nonspecific decrease in activity was found in the retrosplenial posterior cingulate, which is possibly related to default-state activity (also known as resting-state activity). It is difficult to explain the differences between the abovementioned studies that used hypertonic saline to induce muscle pain. Variations in scanning onset relative to hypertonic saline injection onset may play a role. Also, in the studies by Korotkov et al[30] and Thunberg et al,[31] a visual task was performed concomitant with muscle pain. Overall, Kupers et al's findings are more in line with known regions contributing to acute pain processing. Common to all 3 studies is the absence of sensory-discriminative activity in the thalamus, SI and SII during tonic muscle pain. Although this may be speculated to be due to the tonic character of the stimulus, activity in SI and SII have in fact been found in BOLD fMRI studies of tonic pain (see below).

Tonic muscle pain and BOLD fMRI

A series of recent studies employed a novel analysis approach to investigate BOLD fMRI responses to tonic pain stimuli.[33–36] Henderson et al compared responses to tonic pain induced by subcutaneous and intramuscular infusion of hypertonic saline.[33] They found activity in the same cortical areas including somatosensory, insular and cingulate cortices, albeit with some regional differences in signal intensities and cluster locations. Muscle pain but not cutaneous pain evoked a signal intensity decrease in the perigenual cingulate region and signal intensity increases in the primary motor cortex, caudal CMA and anterior insular cortex. In SI, more widespread activity was observed in response to muscle pain. Furthermore, signal intensity increases were observed in the anterior and posterior portions of the mid-cingulate and insular cortex for both cutaneous and muscle pain. These results were largely confirmed in another study but with additional increases in SII and cerebellum and decrease in lateral prefrontal cortex during both tonic muscle and cutaneous pain induced in the forearm as well as in the leg.[34]

Somatotopic organization of the body is necessary for accurate localization of peripheral somatosensory stimuli. Cortical somatotopy has previously been shown to exist for cutaneous pain in SI and posterior insula.[37] However, it is not clear from the previous literature if somatotopic organization also exists for muscle pain. In a recent study, tonic muscle pain induced in the forearm and the leg resulted in similar somatotopy as for tonic cutaneous pain in SI and posterior insula.[34] Additionally, in anterior insula, a somatotopic representation not only existed for both muscle and cutaneous pain but the muscle pain representation was also located more rostral to that of the cutaneous pain. Thus, anterior insula was suggested to subserve encoding of pain (unpleasantness) location as well as pain quality (muscle pain: cramping and dull; cutaneous pain: sharp, pricking and hot).

Muscle pain is perceived as less well-localized than cutaneous pain and is often referred to distant regions of the body. Since SI is known to encode stimulus location and intensity, the more widespread SI activity in response to muscle pain may underlie the perceived spread of pain compared to the more focal cutaneous pain.[33] In Macefield et al's study, a subgroup of subjects exhibiting pain referral also exhibited a greater spread of SI activation.[36] In fact, a positive correlation between peak signal intensity and pain area was observed in a specific SI cluster that only appeared in the referred pain group. Interestingly, this specific area corresponded to the somatotopic representation in SI of the area on the body to which pain was referred. Similar changes were also observed in the anterior insula and cerebellum and an inverse relationship was observed in the perigenual cingulate. As mentioned above, somatotopic organization was previously also observed in the anterior insula for muscle pain and the region specifically engaged during muscle pain may also be related to pain referral.[34]

In summary, tonic muscle pain engages a set of brain regions known to be involved in the processing of pain from other tissue. Several of these regions are also involved in the processing of non-painful stimuli. Finer spatial analysis revealed subtle differences between pain of muscular and cutaneous origin, albeit within the same brain regions. Also, tonic muscle pain may more effectively engage motor-related brain regions including the MI and caudal CMA. The mid-posterior insula is consistently activated during tonic muscle pain. This is in agreement with the posterior insula being among the most frequently observed regions in brain imaging of pain. Although it is a locus that is not exclusively involved in pain processing, lesions encompassing the posterior insula may result in altered pain perception and direct stimulation elicits painful sensations.[38,39] The specific role of the posterior insula remains to be established. Functionally, the posterior insula relies on information related to pain intensity and stimulus location and may be involved in integrating aspects of pain and other somatosensory sensations of different tissue origin. Several other issues are worth mentioning. The activation of SI and SII in the abovementioned fMRI studies and the absence of these 2 regions in all the PET studies using hypertonic saline injection emphasize differences between the 2 imaging modalities, including better spatial and temporal resolution of fMRI compared to PET. The relatively large smoothing kernel used in many PET studies makes it difficult to differentiate among the insula, SII and STG. Another issue is the decreased activity in ACC observed in many of the studies. This was not located homogeneously across studies. Kupers et al[32] found decreased activity in the subgenual cingulate, Thunberg et al[31] in the anterior mid-cingulate, and Henderson et al[33] in the perigenual cingulate. It is unclear if these results represent the same mechanism. Finally, it is worth mentioning that none of the above studies found activity in the thalamus during tonic pain.

Phasic muscle pain and BOLD fMRI

In a series of event-related fMRI studies, phasic muscle pain was induced by IMES.[18,40,41] Phasic muscle pain resulted in a bilaterally distributed network covering the most commonly observed brain regions responding to pain (Figure 2). These regions included the inferior, middle and medial frontal cortices, SI, SII, IPL, STG, anterior, middle and posterior portions of the cingulate and insula, basal ganglia, thalamus, and cerebellum.[18,40] Furthermore, non-painful IMES activated a subset of brain regions engaged by painful IMES.[40] Increases in stimulus intensity have been shown to result in more bilateral engagement of brain regions.[42]

In 2 recent studies, the central effects of hyperalgesia and therapeutic intervention was investigated in patients with myofascial pain syndrome (MPS) using painful IMES in conjunction with event-related fMRI.[18,41] MPS is characterized by local and referred pain emanating from hyperalgesic MTPs. Pain evoked from an MTP was compared to pain from an equivalent site in controls induced by the same stimulus of current magnitude as well as at the magnitude inducing the same subjective pain intensity (Figure 1). Effects associated with hyperalgesia were then revealed by comparing patients and controls at matched current magnitudes while adaptive mechanisms were revealed by comparing patients and controls at matched subjective pain intensity. Hyperalgesia in MPS patients was associated with enhanced activity in regions involved in sensory-discriminative (SI, SII, mid-insula, and IPL) and affective (anterior insula) processing. A highly significant decrease in activity was observed in the dorsal hippocampus. At matched subjective pain intensity, enhanced activity in the same sensory-discriminative regions remained but no anterior insular activity was found. The latter is possibly due to similar levels of pain unpleasantness resulting from the matched pain intensity. Enhanced sensory-discriminative processing is a robust finding in hyperalgesia and allodynia of various etiologies and is not specific to muscular hyperalgesia. Although speculative, adaptive changes in these regions may indicate longer lasting central changes. However, peripheral and spinal influences cannot be ruled out

from the results of this study alone. The meaning of suppressed hippocampal activity in patients with MPS remains unknown. A similar result was found for allodynia in patients with mononeuropathy and in experimentally-induced allodynia by capsaicin.[32,43] The hippocampus is a limbic structure known to process nociceptive-related information. Electrical stimulation of the hippocampus can evoke both pro- and anti-nociception.[44,45] This dual role in analgesia and hyperalgesia is in agreement with a key role in modulating nociceptive responses under acute and chronic stress.[5,46] During acute stress, the hippocampus inhibits brain regions involved in generating the stress response.[47,48] However, stress-related hormones may influence neurotransmission within the hippocampus as well as promote stress-related atrophy leading to impaired function.[49] Moreover, ongoing pain may also serve as an emotional and physical stressor that further promotes chronification.[50] In this context, patients with myofascial pain exhibit exaggerated stress responses in the hypothalamus-pituitary-adrenocortical system.[51]

MPS is difficult to treat effectively on a long-term basis. Several therapeutic interventions provide short-term pain release. A relatively novel approach uses low-intensity (above motor threshold) and low-frequency (2 Hz) electrostimulation within the MTP. This method results in immediate reduction in pain, and long-term effects after periodic intervention include release of sarcomere shortening and the associated ischemia resulting in lasting pain relief. Since the anti-nociceptive effect of non-painful electroacupuncture and transcutaneous electrical stimulation is, at least in part, mediated by the endogenous opioid system, it has been hypothesized that the short-term effects of low-intensity low-frequency IMES within an MTP also engages the opioid system as represented by activation of the periaqueductal grey (PAG) matter in the brain stem.[41] The PAG is a well-known key region in the central pain modulating circuitry. As defined by the change in pain threshold relative to intervention, patients were divided into responders and non-responders to intervention. Interestingly, responders engaged the PAG and affect-regulating regions more effectively than did non-responders during painful IMES to the MTP. Also, the PAG activity was positively correlated with increases in pain threshold across the whole patient group. Thus, individual response to intervention may depend on the capacity to engage the central pain modulatory circuitry. Although several factors were taken into account to avoid expectation of pain relief, this study was not strictly placebo-controlled. In a recent study, placebo analgesia was shown to be mediated by the opioid system.[52]

Conclusions

Since many commonalities between brain processing of cutaneous and muscle pain emerged from these studies, it is reasonable to argue that in the acute state, pain of cutaneous and muscular origins is largely processed in the same brain regions. However, within these regions, finer spatial and temporal analyses revealed subtle differences that may reflect differences at the perceptual level. More substantial differences are likely to be discovered from future work on chronic muscle pain since different types of chronic pain may result in different maladaptive plastic changes. In this respect, chronic muscle pain is often associated with motor dysfunction and stress, which are known to affect specific brain circuits. Suppressed hippocampal function in patients with MPS may represent one such example. More detailed longitudinal studies are needed to monitor the progress of the chronicity process. At present, it remains unknown as to whether or not central changes are reversible and to what degree they contribute to the generation of pain. It is important to find answers to these questions as they may lead to new neural targets for interventions. These targets do not necessarily have to be directly involved in pain processing *per se* since many types of chronic muscle pain have a substantial motor component.

Acknowledgments

This work was supported by grants (NSC 97-2314-B-010-050-MY2, NSC 96-2752-B-010-008-PAE) from the National Science Council, Taiwan, R.O.C.

References

1. Curatolo M, Bogduk N. Pharmacologic pain treatment of musculoskeletal disorders: current perspectives and future prospects. *Clin J Pain* 2001;17:25–32.
2. Witting N, Svensson P, Gottrup H, Arendt-Nielsen L, Jensen TS. Intramuscular and intradermal injection of capsaicin: a comparison of local and referred pain. *Pain* 2000;84:407–12.
3. Curatolo M, Petersen-Felix S, Gerber A, Arendt-Nielsen L. Remifentanil inhibits muscular more than cutaneous pain in humans. *Br J Anaesth* 2000;85:529–32.
4. Travell JG, Simons DG. *Myofascial Pain and Dysfunction. The Trigger Point Manual*. Baltimore: Williams & Wilkins, 1983.
5. Gameiro GH, da Silva Andrade A, Nouer DF, Ferraz de Arruda Veiga MC. How may stressful experiences contribute to the development of temporomandibular disorders? *Clin Oral Investig* 2006;10:261–8.
6. Kumazawa T, Mizumura K. Thin-fibre receptors responding to mechanical, chemical, and thermal stimulation in the skeletal muscle of the dog. *J Physiol* 1977;273:179–94.

7. Stacey MJ. Free nerve endings in skeletal muscle of the cat. *J Anat* 1969;105:231–54.
8. Swett JE, Woolf CJ. The somatotopic organization of primary afferent terminals in the superficial laminae of the dorsal horn of the rat spinal cord. *J Comp Neurol* 1985;231:66–77.
9. Hoheisel U, Lehmann-Willenbrock E, Mense S. Termination patterns of identified group II and III afferent fibres from deep tissues in the spinal cord of the cat. *Neuroscience* 1989; 28:495–507.
10. Cervero F, Iggo A, Ogawa H. Nociceptor-driven dorsal horn neurones in the lumbar spinal cord of the cat. *Pain* 1976; 2:5–24.
11. Mense S, Prabhakar NR. Spinal termination of nociceptive afferent fibres from deep tissues in the cat. *Neurosci Lett* 1986;66: 169–74.
12. Mense S, Craig AD Jr. Spinal and supraspinal terminations of primary afferent fibers from the gastrocnemius-soleus muscle in the cat. *Neuroscience* 1988;26:1023–35.
13. Schomburg ED, Steffens H, Kniffki KD. Contribution of group III and IV muscle afferents to multisensorial spinal motor control in cats. *Neurosci Res* 1999;33:195–206.
14. Wall PD, Woolf CJ. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *J Physiol* 1984;356:443–58.
15. Woolf CJ, Wall PD. Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. *J Neurosci* 1986;6:1433–42.
16. Staahl C, Drewes AM. Experimental human pain models: a review of standardised methods for preclinical testing of analgesics. *Basic Clin Pharmacol Toxicol* 2004;95:97–111.
17. Graven-Nielsen T. Fundamentals of muscle pain, referred pain, and deep tissue hyperalgesia. *Scand J Rheumatol Suppl* 2006; 122:1–43.
18. Niddam DM, Chan RC, Lee SH, Yeh TC, Hsieh JC. Central representation of hyperalgesia from myofascial trigger point. *Neuroimage* 2008;39:1299–306.
19. Niddam DM, Graven-Nielsen T, Arendt-Nielsen L, Chen AC. Non-painful and painful surface and intramuscular electrical stimulation at the thenar and hypothenar sites: differential cerebral dynamics of early to late latency SEPs. *Brain Topogr* 2001;13:283–92.
20. Svensson P, Beydoun A, Morrow TJ, Casey KL. Human intramuscular and cutaneous pain: psychophysical comparisons. *Exp Brain Res* 1997;114:390–2.
21. Torebjork HE, Ochoa JL, Schady W. Referred pain from intraneural stimulation of muscle fascicles in the median nerve. *Pain* 1984;18:145–56.
22. Graven-Nielsen T, McArdle A, Phoenix J, Arendt-Nielsen L, Jensen TS, Jackson MJ, Edwards RH. *In vivo* model of muscle pain: quantification of intramuscular chemical, electrical, and pressure changes associated with saline-induced muscle pain in humans. *Pain* 1997;69:137–43.
23. Babenko VV, Graven-Nielsen T, Svensson P, Drewes AM, Jensen TS, Arendt-Nielsen L. Experimental human muscle pain induced by intramuscular injections of bradykinin, serotonin, and substance P. *Eur J Pain* 1999;3:93–102.
24. Svensson P, Cairns BE, Wang K, Hu JW, Graven-Nielsen T, Arendt-Nielsen L, Sessle BJ. Glutamate-evoked pain and mechanical allodynia in the human masseter muscle. *Pain* 2003; 101:221–7.
25. Svensson P, Graven-Nielsen T, Arendt-Nielsen L. Mechanical hyperesthesia of human facial skin induced by tonic painful stimulation of jaw muscles. *Pain* 1998;74:93–100.
26. Malone MD, Kurtz RM, Strube MJ. The effects of hypnotic suggestion on pain report. *Am J Clin Hypn* 1989;31: 221–30.
27. Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiol Clin* 2000;30:263–88.
28. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 2005;9:463–84.
29. Svensson P, Minoshima S, Beydoun A, Morrow TJ, Casey KL. Cerebral processing of acute skin and muscle pain in humans. *J Neurophysiol* 1997;78:450–60.
30. Korotkov A, Ljubisavljevic M, Thunberg J, Kataeva G, Roudas M, Pakhomov S, Radovanovic S, et al. Changes in human regional cerebral blood flow following hypertonic saline induced experimental muscle pain: a positron emission tomography study. *Neurosci Lett* 2002;335:119–23.
31. Thunberg J, Lyskov E, Korotkov A, Ljubisavljevic M, Pakhomov S, Katayeva G, Radovanovic S, et al. Brain processing of tonic muscle pain induced by infusion of hypertonic saline. *Eur J Pain* 2005;9:185–94.
32. Kupers RC, Svensson P, Jensen TS. Central representation of muscle pain and mechanical hyperesthesia in the orofacial region: a positron emission tomography study. *Pain* 2004;108:284–93.
33. Henderson LA, Bandler R, Gandevia SC, Macefield VG. Distinct forebrain activity patterns during deep versus superficial pain. *Pain* 2006;120:286–96.
34. Henderson LA, Gandevia SC, Macefield VG. Somatotopic organization of the processing of muscle and cutaneous pain in the left and right insula cortex: a single-trial fMRI study. *Pain* 2007;128:20–30.
35. Henderson LA, Gandevia SC, Macefield VG. Gender differences in brain activity evoked by muscle and cutaneous pain: a retrospective study of single-trial fMRI data. *Neuroimage* 2008;39:1867–76.
36. Macefield VG, Gandevia SC, Henderson LA. Discrete changes in cortical activation during experimentally induced referred muscle pain: a single-trial fMRI study. *Cereb Cortex* 2007;17: 2050–9.
37. Brooks JC, Zambreanu L, Godinez A, Craig AD, Tracey I. Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. *Neuroimage* 2005;27:201–9.
38. Greenspan JD, Lee RR, Lenz FA. Pain sensitivity alterations as a function of lesion location in the parasylvian cortex. *Pain* 1999;81:273–82.
39. Ostrowsky K, Magnin M, Ryvlin P, Isnard J, Guenot M, Mauguiere F. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cereb Cortex* 2002;12:376–85.
40. Niddam DM, Yeh TC, Wu YT, Lee PL, Ho LT, Arendt-Nielsen L, Chen AC, et al. Event-related functional MRI study on central representation of acute muscle pain induced by electrical stimulation. *Neuroimage* 2002;17:1437–50.
41. Niddam DM, Chan RC, Lee SH, Yeh TC, Hsieh JC. Central modulation of pain evoked from myofascial trigger point. *Clin J Pain* 2007;23:440–8.
42. Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol* 1999;82:1934–43.
43. Petrovic P, Ingvar M, Stone-Elander S, Petersson KM, Hansson P. A PET activation study of dynamic mechanical allodynia in patients with mononeuropathy. *Pain* 1999;83:459–70.
44. Halgren E, Walter RD, Cherlow DG, Crandall PH. Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdala. *Brain* 1978;101:83–117.
45. Prado WA, Roberts MH. An assessment of the antinociceptive and aversive effects of stimulating identified sites in the rat brain. *Brain Res* 1985;340:219–28.

46. Bodnar RJ, Kelly DD, Brutus M, Glusman M. Stress-induced analgesia: neural and hormonal determinants. *Neurosci Biobehav Rev* 1980;4:87–100.
47. Feldman S, Conforti N. Participation of the dorsal hippocampus in the glucocorticoid feedback effect on adrenocortical activity. *Neuroendocrinology* 1980;30:52–5.
48. Fendler K, Karmos G, Telegdy G. The effect of hippocampal lesion on pituitary-adrenal function. *Acta Physiol Acad Sci Hung* 1961;20:293–7.
49. Sousa N, Lukoyanov NV, Madeira MD, Almeida OF, Paula-Barbosa MM. Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement. *Neuroscience* 2000; 97:253–66.
50. Duric V, McCarson KE. Persistent pain produces stress-like alterations in hippocampal neurogenesis and gene expression. *J Pain* 2006;7:544–55.
51. Yoshihara T, Shigeta K, Hasegawa H, Ishitani N, Masumoto Y, Yamasaki Y. Neuroendocrine responses to psychological stress in patients with myofascial pain. *J Orofac Pain* 2005;19:202–8.
52. Zubieta JK, Bueller JA, Jackson LR, Scott DJ, Xu Y, Koeppe RA, Nichols TE, et al. Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *J Neurosci* 2005;25: 7754–62.