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Functional imaging and the neural systems of chronic pain

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Pain affects hundreds of millions of people worldwide and is the primary complaint resulting in physician visits and health care resource use [1]. The importance of pain as a major worldwide health care problem has been recognized by the World Health Organization [2], and the need for further research into its mechanisms and control was recognized by the US Congress in its declaration of the years 2001 through 2010 as the "Decade of Pain Control and Research" [3].

The presence of pain and its inadequate treatment in a variety of clinical settings have a significant societal impact. Pain contributes to the overall economic burden of disease through increased direct medical costs caused by additional health care resource use. Furthermore, pain has been reported to be the primary reason for absenteeism and on-the-job loss of productivity, resulting in high indirect costs [4]. It has been estimated that the cost of health care, compensation, and litigation resulting from pain is more than $100 billion annually in the United States [5].

In addition to direct and indirect costs, pain has a significant impact on individuals and their families, affecting functionality and quality-of-life parameters that are difficult to measure and place a value on.

Despite significant progress in the understanding of the molecular and cellular mechanisms of pain, there are still millions of people who live with chronic pain.

Pain versus nociception

Pain has been defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [6]. This definition characterizes pain as a subjective experience that is private and specific to the individual involved. Unfortunately, unlike many diseases we treat, such as hypertension or diabetes, there is no direct reproducible measurement we can make to measure a patient's pain. We are left with the notion that pain is whatever the patient tells us and attempting to correlate our objective measurements (physical examination findings, imaging results, and laboratory tests) with the subjective data. Further complicating the problem is the notion that in the clinical arena, pain is often confused with the concept of nociception, which are the neural signals generated and transmitted to the spinal cord and brain in the face of stimuli that are tissue damaging or potentially tissue damaging. Pain, in contrast, requires an intact brain present to process these

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nociceptive signals and translate them into a subjective experience.

The distinctions between nociception and pain are of particular relevance when discussing chronic pain states in which there may be the presence of pain but without evidence of tissue damage. These nonnociceptive or neuropathic pain conditions are often the result of damage or abnormal activity within the neural systems involved with the nociceptive transmission circuits or the pain modulatory circuits within the spinal cord or brain. Indeed, it is damage to the same peripheral and central pain pathways that conveys nociceptive signals to warn us of actual or potential tissue damage. In the case of neuropathic pain, however, these signals have no beneficial survival value to impart. These neuropathic pain conditions are insidious in that they are often associated with depression, anxiety, decreased libido, altered appetite, and sleep disturbances [7].

Neuropathic pain can result from injury or trauma (eg, surgery), infection (eg, postherpetic neuralgia), endocrine disorders (eg, diabetes, hypothyroidism), demyelination (eg, multiple sclerosis), errors in metabolism, degenerative disorders (eg, Parkinson's disease), or damage directly to the spinal cord or brain (eg, thalamic stroke) [7]. As an example of neuropathic pain, a patient who experiences a thalamic stroke may complain of deep aching pain within his/her arm (thalamic pain syndrome) that the patient believes is being caused by a torn muscle. This helps to explain the portion of the IASP pain definition that includes "or described in terms of such damage." Although the previously mentioned neuropathic pain states are traditionally thought of as having a centralized component, recent investigation using functional neuroimaging techniques demonstrates that chronic pain conditions commonly thought to be primarily a nociceptive problem may have a large centralized component. These conditions, which include chronic low back pain (CLBP), fibromyalgia, irritable bowel syndrome, and complex regional pain syndrome (CRPS)/reflex sympathetic dystrophy (RSD), are discussed later in this article.

Experimental pain models

The development of experimental pain models has contributed significantly to our knowledge of supraspinal mechanisms of pain. Animal models of pain have been used extensively based on the premise that these models can serve as surrogate assays that allow us to understand the mechanisms of pain and predict the efficacy of pharmacologic agents [8]. In contrast to the polymorphic nature of pain that is described in human beings, pain in animals can only be examined by their reactions to various chemical, thermal, and mechanical stimuli, with the latency or nature of response altered in the "pain" state [9]. The published reports on animal models of pain are mostly represented by acute and tissue injury models [10]; of these, the tail-flick and hot-plate tests remain the most commonly used, with a progressive increase in the use of the formalin model and the various tests that involve withdrawal of the paw from mechanical stimuli or tactile allodynia (ie, the abnormal response and change in threshold to nonnoxious stimuli) [10]. In addition, tests that are usually based on intradermal or intraperitoneal injections of an irritant or foreign chemical agent as the nociceptive stimulus are used as models of tonic pain and not of chronic pain, because the duration of the behaviors is short, usually minutes or tens of minutes. Intracapsular administration of urate crystals, Freund's adjuvant, capsaicin, or carrageenin for weeks [11–13] is closely related to models of tonic pain but is used as a chronic inflammatory pain model [14,15]. Finally, a variety of animal pain models have been developed that use injuries to peripheral nerves, such as the sciatic nerve, or to the spinal cord to produce temporary or permanent behavioral hypersensitivity, such as allodynia or hyperalgesia (ie, a decrease in the latency of response to normally noxious stimuli) [9]. Hypersensitivity caused by peripheral nerve injury develops over several days after the injury and can lead to chronic pain [16]. In pain patients, especially those with below-level pain after complete spinal transsection, there can be a dissociation between reported chronic pain and elicited nociception that is not possible to differentiate in animals [17,18]. In summary, whereas animal models have contributed much to the understanding of the mechanisms of pain in human beings, applying findings from animal studies to clinical states of pain must be interpreted with caution. The animal models do not capture the complex pain experience that includes psychophysiologic, psychologic, and environmental factors. (For an excellent review of animal pain models, the reader is referred to the article by Le Bars et al [10]).

Taking these factors into account, human pain models may act as a bridge between animal

research and understanding the mechanisms underlying clinical pain states. Studies of human pain models are of significant importance in that one can study the cognitive and affective aspects that are often difficult if not impossible to determine with animal pain models. Research of human pain models also has an advantage over studies of clinical populations. Many prevalent pain disorders are "multifactorial" or "complex," that is, they develop from the combined action of many genes, risk-conferring behaviors, gender, culture and environmental factors (eg, medication or other forms of treatment), and comorbid diseases [19]. Although clinical studies are important and yield valuable findings, such research is often compromised because of this complexity. Because the links between peripheral pathology; central neurobiology; and the associated sensory, motor, autonomic, mood, and cognitive signs and symptoms are unknown, experimental pain models provide insight into complex processes of clinical pain by simplifying and parsing out the multifactorial processes involved in pain. Human pain models often use noxious thermal and electrical pulses, topical or intradermal injection of the irritant capsaicin [20], or third molar extractions [21]. Different human pain models, however, induce distinctly different pain attributes and thereby approximate processes that may or may not be universally applicable to all clinical pain conditions. This needs to be taken into account when studying pain processing using human pain models [9]. Therefore, an integrative approach using various experimental pain models as well as clinical populations is necessary in understanding the physiologic, anatomic, and functional properties of pain processing. To this end, recent advances in functional imaging are of particular interest, because functional imaging provides us with means to bridge between animal and human pain models and clinical pain states. It allows us to investigate the neural plastic changes that occur in chronic pain conditions more fully; to account for the complex cognitive, emotional, and environmental influences on pain; and to study the effects of therapies on the perception of pain.

Central processing and perception of pain

As we all know from our own experience, our perception of pain is not directly proportional to the extent of the injury or the intensity of the painful stimuli being applied. The gate-control theory, which was first proposed by Melzack and Wall [22] in 1965, explains this phenomenon and states that nerve impulses evoked by injury are influenced in the spinal cord by other nerve cells that act like gates, either preventing the impulses from getting through or facilitating their transmission. Large- and small-diameter nerve fibers project to the substantia gelatinosa of the spinal cord, which, in turn, projects nerve fibers to the central nervous system (CNS), where these signals are integrated. Whereas small-diameter nerve fibers (nociceptive fibers) have an excitatory input, large-diameter nerve fibers have an inhibitory input onto spinal cord transmission cells, which project into the CNS. Small-fiber afferent pain stimuli can be modulated by these large-fiber afferent stimuli and other descending spinal pathways so that their transmission to ascending spinal pathways is blocked (gated).

More specifically and from a neuroanatomic and physiologic perspective, noxious stimuli are transmitted from the peripheral nociceptor through thinly myelinated Aδ and unmyelinated C-fibers that terminate in the dorsal horn of the spinal cord [23]. Neurons in the dorsal horn responding to noxious stimuli are located in the superficial aspects of the dorsal horn (lamina I), whereas wide dynamic range (WDR) neurons responding to noxious and nonnoxious stimuli are located in the deeper dorsal horn (lamina IV and V) [24]. Axons from secondary interneurons cross the midline within one or two segments and ascend in spinal-cortical pathways, with the most commonly recognized being the spinal thalamic tract (STT). Axons in the lateral STT originate mainly from lamina I neurons, whereas anterior STT axons originate from deeper dorsal horn neurons. Nociceptive signals continue to course cephalad until they synapse in the thalamus. Thalamic nuclei then project the nociceptive signals to cortical and subcortical targets, where further processing occurs, finally resulting in the perception of pain. At all levels, these ascending nociceptive signals may be modulated by descending projections.

There is a substantial neurophysiologic literature exploring the central representation of pain [25,26] by brain regions associated with sensory, discriminatory, affective, and motivational functions, comprising a "pain matrix" of brain regions [25,27,28]. Indeed, methods other than functional neuroimaging have provided significant information regarding the role of supraspinal structures in

the processing and perception of pain. Electrophysiologic techniques and anatomic tracing methods have confirmed and expanded on many of the classic pathways and revealed a multitude of additional ascending and descending tracts and structures [7].

It has been proposed that the pain matrix comprises at least two main systems working in parallel called the lateral and medial pain systems [27]: the lateral pathway is responsible for communicating the sensory-discriminative components of pain, and the medial pathway is responsible for the affective, motivational, attentional, and evaluative components of pain processing. Recent animal studies reveal that the ascending nociceptive and descending modulatory pathways may contribute to the affective-motivational aspects of pain and play a critical role in the modulation of pain [29–34]. In addition to the classic spinothalamocortical nociceptive projections, there is a nociceptive pathway that originates in the dorsal horn of the spinal cord, ascending to the dorsocaudal medulla (subnucleus reticularis dorsalis), then to the ventromedian nucleus of the thalamus, and finally to the dorsolateral frontal lobes [35]. Other pathways project from the spinal cord to the hypothalamus and amygdala via the parabrachial nucleus [36,37], to the frontal cortices via the parabrachial nucleus and intralaminar thalamus [38–40], and to the basal forebrain via the parabrachial nucleus and the central nucleus of the amygdala [38,39]. Descending pathways project from pain-related cortical areas, such as the somatosensory areas, the insular cortex, and the medial prefrontal cortex (PFC) to the periaqueductal gray (PAG) [41,42]. In addition, descending projections are found from multiple areas of the anterior cingulate cortex (ACC), an area that receives spinothalamocortical nociceptive input [29]. Recent work on pain-induced avoidance behavior [43–45] and opioid- and cannabinoid-dependant pain modulation [46,47] shows the role of higher order cerebral structures, such as the amygdala and rostral ACC in receiving and integrating nociceptive information to regulate behavior. Other areas, such as the PAG, nucleus raphe magnus, insular cortex, and medial PFC, also play key roles in descending mechanisms that modulate spinal nociceptive activity [33,48–52]. These networks of brain regions may contribute to the cognitive and affective aspects of pain and to the interactions between the sensation of painful stimuli, subjective perception of pain, and cognitive and affective processes that modulate the perception of pain (Fig. 1) [53].

Significance of functional imaging research

Functional neuroimaging studies of pain in human beings provide us with an opportunity to study the normal and abnormal pain mechanisms and the multidimensional experience of pain influenced not only by the nociceptive signals but by the central mechanisms of attention, anticipation, mood, and memory of past experiences, which are all known to influence the perception of pain. Isolating each of these factors has been challenging, and discrepancies in the results of some of the earlier imaging studies may have resulted from difference in various methodologic issues, such as imaging techniques, behavioral and psychophysical measures, populations studied, and type of pain studied. Proper design of neuroimaging studies to isolate and control for the sensory, cognitive, and affective factors is essential to achieve interpretable results. With increasing collaboration across disciplines, such as anatomy, anesthesiology, cognitive neuroscience, neurology, neurosurgery, and physiology, neural mechanisms of pain are becoming better understood. Findings from functional neuroimaging studies may not only fill the gap between the results from animal and human research but may yield important information to guide new directions in clinical practice.

Functional neuroimaging of pain

Brain regions involved in pain perception

Recent investigations using functional imaging techniques (functional magnetic resonance imaging [fMRI], positron emission tomography [PET], single-photon emission computed tomography [SPECT], high-density electroencephalography [EEG], and magnetoencephalography [MEG]) have identified a variety of cortical and subcortical structures involved with the cerebral response to nociceptive stimuli in human beings. These structures include the primary (S1) and secondary (S2) somatosensory cortices, thalamus, ACC, and insular cortex [54–77]. Less commonly found, and still somewhat controversial, are areas like the supplementary motor area (SMA), premotor cortex, PFC, parietal cortex, midbrain, basal ganglia, amygdala, cerebellum, and striatum (Fig. 2) [55,59–64,66,69,71,73,75–85].

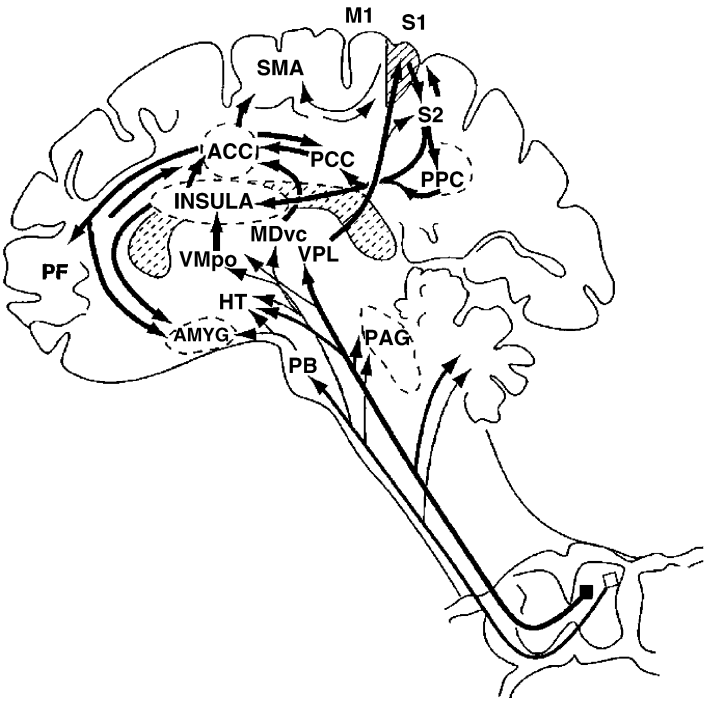

Fig. 1. (*Top*) A schematic used to illustrate interactions between pain sensation, pain unpleasantness, and secondary pain affect (*solid arrows*). Neural structures likely to have a role in these dimensions are shown. Nociceptive or endogenous physiologic factors that influence pain sensation and unpleasantness (*dashed arrows*) are shown. (*Bottom*) Schematic of ascending pathways, subcortical structures, and cerebral cortical structures involved in processing pain. PAG, periaqueductal gray; PB, parabrachial nucleus of the dorsolateral pons; VMpo, ventromedial part of posterior nuclear complex; MDvc, ventrocaudal part of the medial dorsal nucleus; VPL, ventroposterior lateral nucleus; ACC, anterior cingulated cortex; PCC, posterior cingulated cortex; HT, hypothalamus; S1 and S2, first and second somatosensory cortical areas; PPC, posterior parietal complex; SMA, supplementary motor area; AMYG, amygdala; PFC, prefrontal cortex. (*From* Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science 2000;288(5472):1769–72; with permission.)

The levels of activation of some of these structures found to be related to pain have been shown to correlate with subjects' perception of pain intensity and/or unpleasantness, suggesting that coding of pain perception occurs or is related to these structures. Regions that correlated with pain perception are the ACC [80,86,87]; posterior cingulate cortex [80]; contralateral S1 [86,87] and S2 [59,60,86]; medial PFC [80,87]; insular cortex [87]; parietal [59,60,80], SMA [80,86], motor cortex (MI) [80,86], and premotor areas [80,86]; cerebellum [86]; putamen [86]; thalamus [86]; and PAG (Fig. 3) [70]. Further support of the ACC being involved in pain perception are studies of hypnotic suggestion [88,89], which showed that specific manipulation of pain unpleasantness produces significant changes in the ACC. In addition, a recent study found that highly sensitive versus lowly sensitive individuals show greater activity in the S1, ACC, and PFC in the high-sensitivity group [76]. These findings are consistent with studies on patients who received neurosurgical deafferentation of the ACC for chronic intractable pain, which reported that persistence of the experience of pain with the affective impact diminished [90], supporting the interpretation that BA24/ACC areas are associated with subjective changes in pain unpleasantness. With regard to pain intensity and not unpleasantness, manipulation of pain intensity produces changes mainly in the S1 [91], S2 [71] and insular cortex [71].

Although part of the discrepancies in the results may be attributed to the difference in imaging methods, pain stimuli applied, and psychophysical and behavioral measurements obtained, these regions have repeatedly been shown to be involved in pain processing. With regard to the motor regions, there is some debate as to

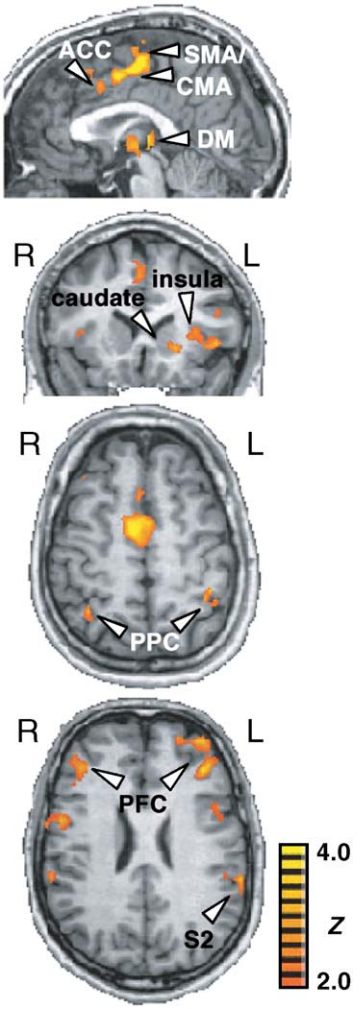

Fig. 2. Prickle-related activities. The major areas of prickle-related activity (*white arrows*) were located in the medial wall (anterior cingulate cortex [ACC], supplementary motor areas [SMA] and cingulate motor areas [CMA], dorsomedial thalamus [DM]; sagittal slice, × = -1); caudate and insular (coronal slice, y = 16); and second somatosensory cortical area (S2), posterior parietal cortex (PPC), and prefrontal cortex (PFC) (upper axial slice, z = 49; lower axial slice, z = 26). (*From* Davis KD, Pope GE, Crawley AP, Mikulis DJ. Neural correlates of prickle sensation: a percept-related fMRI study. Nat Neurosci 2002;5(11):1121-2; with permission.)

whether these regions are related to the preparatory and motor responses to withdrawal when pain is applied. In addition, some have thought that the ACC is not specifically involved in pain perception but in the attention-demanding nature of pain (see references [88–90,92] for findings against this claim). As the experimental designs become more sophisticated, specifically targeting the cognitive and affective components of interest, neural circuitry involved in (1) the sensory and affective components of pain perception, (2) different types of pain, (3) abnormal and normal pain responses, and (4) the modulation of the perception of pain are likely to be identified.

Spinal cord and brain stem imaging

The spinal cord and brain stem are critical centers for nociceptive processing before sending signals to the brain. They are also sites for significant functional abnormalities in chronic pain states. Unfortunately, there are serious challenges in using fMRI in these regions of the CNS, which is why most neuroimaging studies have involved the brain. Difficulties in measuring the blood oxygen level–dependent (BOLD) response arise from periodic pulsatory motion of the cerebrospinal fluid (CSF) that surrounds the spinal cord and brain stem as well as from periodic respiratory and pulsatile cardiac movement. This leads to degradation of the magnetic resonance signal and to motion artifact. These problems are compounded by the relatively small diameter of the spinal cord.

Recently, these challenges to spinal cord imaging have been overcome by our laboratory [93] as well as others [94,95]. Using a 3-T MRI system, we have demonstrated the ability to image dorsal horn activation to thermal nociceptive stimuli with a resolution adequate to differentiate superficial and deep dorsal horn structures. Appropriate somatotopic representation of activation in the cervical spinal cord to thermal and cold stimuli has been achieved. In a recent study, noxious thermal stimuli were applied to the right and then left lateral aspects of the forearm and similarly in the deltoid region. Fig. 4 illustrates the results of BOLD activation in the cervical spinal cord. Further work is underway to investigate the effects of plasticity in models of experimental and clinical pain.

The ability to image the whole pain pathway in a single individual would provide a tremendous opportunity to evaluate the changes in disease state and response to peripherally and centrally acting treatments. Although this has not yet been done in the spinal cord–brain stem–brain axis, some preliminary work has been reported in neuroimaging the trigeminal system and brain. The trigeminal nucleus is the functional equivalent

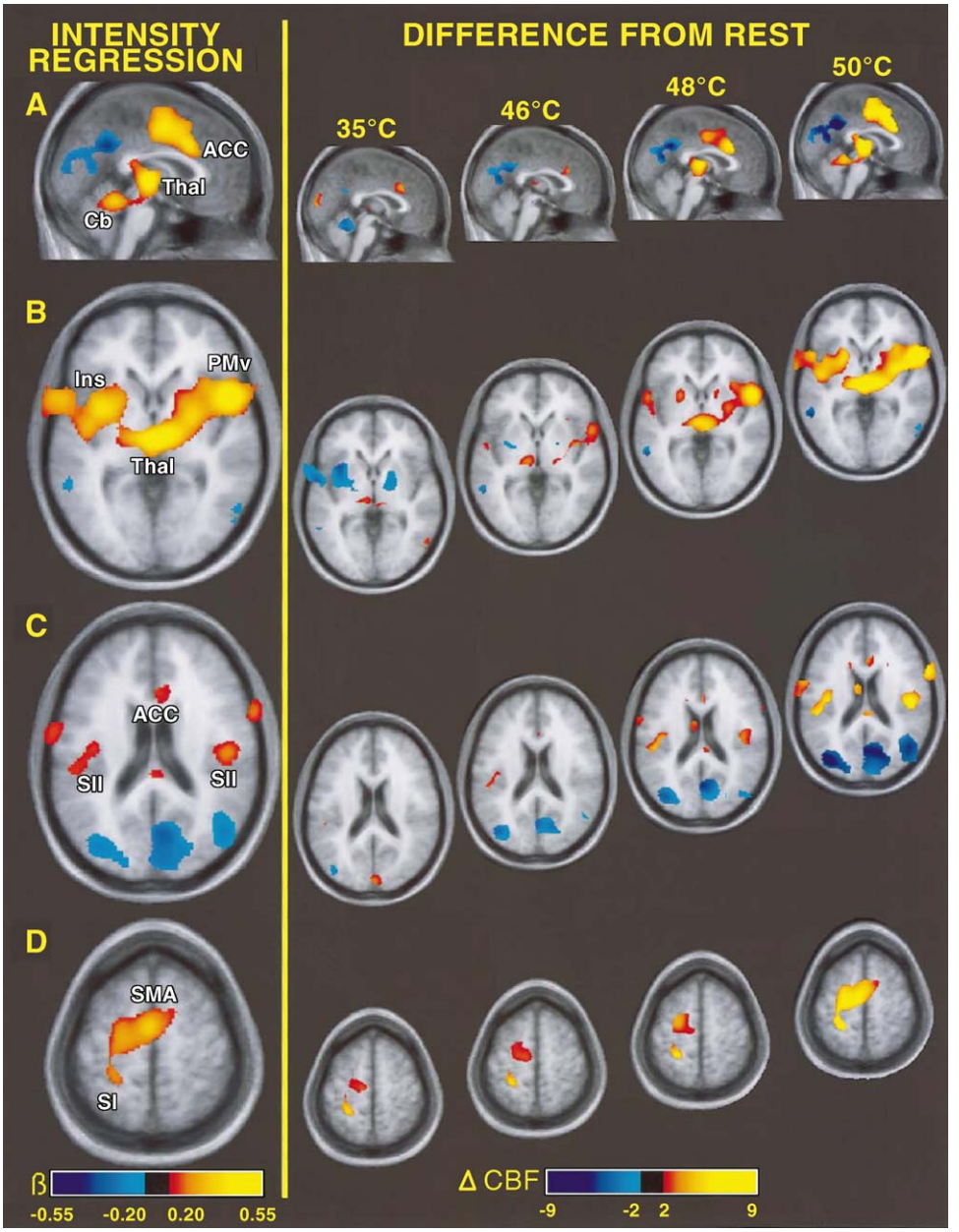

Fig. 3. Multiple regression analysis reveals that activation within a diverse array of brain areas is significantly related to subjects' perceptions of pain intensity (*left panel*: regression coefficients (B) are color coded such that red-yellow voxels are positively related to pain intensity, whereas blue-violet voxels are inversely related to pain intensity; $P < 0.001$). Progressive increases in activation are evident within these areas as stimulus temperature increases (*right panel:* cerebral blood flow [CBF] difference between each temperature and rest). Functional data are displayed on the averaged structural MRI data of all subjects. The left side of the image corresponds to the subjects' left. ACC, anterior cingulate cortex; Thal, thalamus; Cb, cerebellum; Ins, insula; PMv, ventral premotor cortex; SII (S2), secondary somatosensory cortex; SI (S1), primary somatosensory cortex; SMA, supplementary motor area. (*From* Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. J Neurophysiol 1999;82(4):1934–43; with permission.)

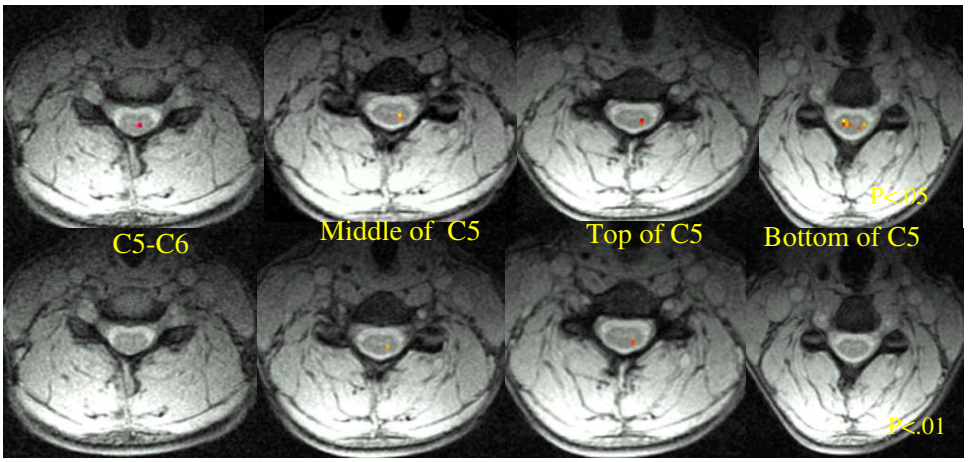

Fig. 4. Blood oxygen level–dependent response to thermal stimulation of the left lateral forearm in the cervical spine. At $P < 0.05$ (*top panel*), multiple activations are seen in the ipsilateral and contralateral dorsal horn as well as in the ventral horn. As the probability value becomes more stringent ($P < 0.01$, *bottom panel*), the contralateral activations disappear and the remaining activations center around the middle to top of C5. Images are in radiologic convention.

to the dorsal horn in the spinal cord and has recently been mapped using fMRI. Borsook et al [96,97] have made significant progress in mapping the somatotopic representation of the face in the trigeminal nucleus to noxious thermal stimulation.

Significant work is required to make human spinal cord and brain stem imaging a useful research and clinical tool. Once the technical hurdles have been overcome, the ability to image the neural axis from the spinal cord to the brain and descending modulatory pathways back to the spinal cord is likely to present an exciting opportunity to investigate the plasticity changes associated with chronic pain conditions. Furthermore, connectivity studies should provide additional information about the functional network in normal and disease states.

Cognitive and emotional modulation of pain experience

The sensory and affective components of pain are often found to correlate well with the degree of noxious stimulation. It is clear, however, that the experience of pain can be significantly modulated by our own thoughts and feelings and is not directly a linear phenomenon. Several specific factors that modulate our perception of pain have been identified, including attention, anticipation, and mood. Each of these has been shown to influence the way we respond to pain, and there are an increasing number of functional neuroimaging studies investigating how these factors affect pain perception and activity in the brain.

Effects of attention on pain

There have been anecdotal accounts for centuries of people experiencing traumatic injuries and apparently experiencing little or no pain—events that most of us would find excruciatingly painful. Furthermore, it is well established that distracting away from a noxious stimulus results in a decreased perception of pain [98], which is a technique used in the management of chronic pain patients that takes many forms, such as walking the dog, listening to music, reading a book, and working. Attention to a different task or cognitive distraction has been shown to attenuate activity in the ACC, insular cortex, thalamus, somatosensory regions, and PAG [70,99–103]. These studies have either asked the subjects to distract away from their painful stimulus [70,101], to perform a concomitant distracting computer maze task [99] or a counting Stroop task [103], or to attend to a countervibratory stimulation [100] or an auditory stimulus [102].

Attention to pain, however, has produced mixed results, sometimes enhancing pain perception when, for example, manipulating the frequency of rating pain [104]. Paradoxically, it has led to a reduction in perceived pain in male subjects during a cold-pressor pain test [105] or in health-anxious chronic pain patients [106]. This paradox may be partly a result of the attention-

demanding nature of pain [98] and potentially of differences between normal subject populations versus pain patients [107].

The precise neural mechanisms underlying attentional modulation of the pain experience are not known. There are data that suggest involvement of multiple levels of the CNS. One such system is the opiate-sensitive descending and ascending pathways: a pathway from the frontal cortex to the amygdala, PAG matter, rostral ventral medulla, and, finally, dorsal horn of the spinal cord [51,103] as well as ascending pathways through the medial thalamus to the ACC [89,108–110]. Although attentional modulation of nociceptive neural activity and pain perception has been observed in the medullary dorsal horn of the spinal cord in a number of neurophysiologic studies [108,111], it has not been shown in functional neuroimaging studies.

Although the data are limited, studies have demonstrated that patients with chronic pain have an impaired ability to distract from their chronic pain independent of their pain intensity [107]. These studies strongly suggest cortical or subcortical dysfunction as a cause for this impairment, with probable areas including the orbitofrontal cortex (OFC) and ACC. Further study is needed to elucidate the neural mechanisms and the connectivity between brain systems involved to help guide pharmacologic and cognitive-behavioral treatments.

Effects of anticipating pain

When we anticipate pain, we experience fear and anxiety. Anticipation is different from the experience of pain itself as well as from a general experience of fear or anxiety. Expectation and anticipation of pain are known to influence the immediate unpleasantness of pain [48,112,113]. Uncertain pain has been demonstrated to increase unpleasantness and to result in less pain tolerance compared with certain pain [114]. This may involve several factors, such as cognitive appraisal, arousal, conditioning and orienting, or diverging attention from the source and site of noxious input, and may vary depending on the instructions given to the subjects and their past experience [113]. There is also evidence in human beings that acute stress can activate the pain-modulating circuit that contributes to analgesia [51]. This may be achieved by the stress regulatory systems, including endocrine, autonomic, immune, and opioid systems [25,115]. It has previously been difficult to dissociate these experiences in functional neuroimaging studies. Recently, however, a small number of studies examined the neural mechanism underlying the anticipation of pain. Expectation of pain activated the medial frontal lobe, insular cortex, and cerebellum, which were neighboring but not actual locations mediating the pain experience itself [112]. Another study showed that subjects who anticipated a noxious stimulus showed downregulation of activity in the ACC and medial OFC during pain anticipation, whereas subjects who did not know what to expect showed an increased activity in similar regions in addition to the PAG [114]. The amygdala has also been shown to be involved in the expectation of noxious stimuli [51]. Subsequent studies, however, suggested that these responses could be blocked by nonanalgesic benzodiazepines and thus may be more related to anxiety than to anticipation of pain per se [27]. More recently, it has been shown that most of the nociceptive system can be activated by anticipation of a painful stimulus [87]; the anticipatory responses are just smaller than the pain intensity–related responses [28].

Anticipation of pain seems to differentially recruit brain regions related to pain, its adjacent regions, and regions related to emotion regulation. Because anticipation of pain is a common phenomenon in chronic pain patients and may be maladaptive, these studies may be useful in developing new treatments.

Effects of placebo

Interestingly, high concentrations of opioid receptors are found in the medial pain system, including the rostral ACC and medial thalamus [115–117]. Most of the changes that occur in opioid receptor binding in acute and chronic pain are within this medial system [118–120]. In line with this literature and literature suggesting that placebo analgesia may be at least partially mediated by endogenous opioid peptides [121,122], the rostral ACC was activated for opioid and placebo analgesia [123,124]. Activity of the ACC covaried with activity of the PAG. These results fit well with the findings that the descending systems via the PAG may depress mean discharge rates of nociceptive spinal dorsal horn neurons and that there exist antinociceptive heterosegmental interneurons that may be activated by noxious stimulation or by supraspinal descending pathways [125–127]. These mechanisms seem to contribute to the endogenous pain-controlling systems. A more recent study investigated the existing

controversy as to whether placebos alter sensory pain transmission and pain affect or simply produce compliance with the suggestions. Placebo analgesia was shown to be related to decreased brain activity in pain-sensitive brain regions, including the thalamus, insular cortex, and ACC, and was associated with increased activity during anticipation of pain in the PFC [128]. This study provides more direct evidence that placebos alter the experience of pain.

Effects of mood on pain

Mood and emotional states have also been shown to alter pain perception, although dissociation of mood and attention has been difficult and may have confounded previous reports. Manipulations that have a positive effect on mood or emotional states, such as pleasant music, pleasant pictures, and humorous films, generally reduce pain perception [129–134]. Manipulations that have a negative effect on mood or emotional state, however, have not always been consistent [129–132].

Recent research indicates that people who are fearful of pain tend to report more negative pain experiences. Those with a high fear of pain exhibited a selective attentional bias toward pain-related information compared with those classified as low in the fear of pain [135]. These results indicate that one reason why those with a high fear of pain are particularly susceptible to negative pain experiences could be the result of biased attentional processes. To our knowledge, there are no functional neuroimaging studies that have directly manipulated mood states to examine their influence on the perception of pain and activated brain regions. One study, however, examined the neural mechanisms underlying the effect of emotional context on visceral sensation [136]. Activation within the right insular and bilateral dorsal ACC was significantly greater during esophageal sensation with fearful rather than neutral faces. In addition, significantly greater discomfort to esophageal sensation, anxiety, and activation predominantly within the left dorsal ACC and bilateral anterior insular cortices occurred with high-intensity compared with low-intensity expressions. This shows evidence that the intensity of the negative emotional context modulates neural responses and perceived discomfort during nonpainful visceral stimulation, which may help us to understand the mechanism underlying how mood affects the perception of pain in patients with pain disorders. This study may also have implications in the neural mechanism underlying allodynia.

Studies on the attentional, anticipatory, and other cognitive modulations of pain together with the biochemical and anatomic understanding of analgesia provide us with insights into the top-down and bottom-up plastic changes that occur in the CNS. Functional neuroimaging research in this area has just begun, concentrating on the interplay between affect and pain perception. Future research using functional neuroimaging in this area is warranted and is likely to have a significant impact on cognitive and other therapeutic interventions.

Neuroimaging of allodynia and hyperalgesia

Most of our clinical chronic pain conditions are associated with increased sensitivity to external stimuli, including touch, pressure, heat, cold, and movement. These phenomena represent reduced sensory thresholds for producing pain and are referred to as allodynia when the pain is caused by a normally nonpainful stimulus and hyperalgesia when there is an increased perception of pain to a painful stimulus. We have previously discussed some of the animal models used to investigate these phenomena. Human pain models have been developed to investigate pharmacologic interventions, and they have been shown to share some characteristics with neuropathic pain [137–139]. These models have recently been extended to use neuroimaging to investigate the CNS effects of experimentally induced allodynia and hyperalgesia. Topical or intradermal capsaicin inducing secondary hyperalgesia has been a commonly used model in an attempt to replicate the neural plastic changes thought to occur with neuropathic pain [20]. Iadarola et al [140] used PET to image pain induced by capsaicin injection and compared it with activations resulting from lightly brushing the treated area after the pain had resolved. Subjects described pain consistent with allodynia to light brushing, with corresponding activation throughout the pain matrix. A similar study followed using fMRI and achieved equivalent results using mechanical allodynia [141]. More recently, heat allodynia was induced using capsaicin in volunteers and compared with heating of normal skin. The intensities of the stimuli were maintained the same. The results suggested that different central pathways were responsible for the sensation of pain in the experimental allodynia

condition compared with the heated normal skin. The investigators identified unique activations of the medial thalamus, dorsal midbrain, contralateral right ventral putamen, right anterior insula, perigenual cingulate cortex, PFC, and OFC. They hypothesized that some of the differences were attributable to the greater unpleasantness of the capsaicin-induced allodynia but that the differences were also a result of the unique peripheral and central mechanisms responsible for pain caused by injury, inflammation, and other pathologic conditions. These results, which need to be replicated and expanded, are likely to help advance neuroimaging as a tool to confirm or negate the efficacy of experimental pain models and to provide additional measures of pharmacologic treatment effectiveness.

Neuroimaging chronic pain states

Evidence suggests that generation and maintenance of chronic pain, as opposed to acute pain, involves changes in central pain processing mediated through mechanisms of neural plasticity and ultimately leading to hyperexcitability of central structures [142,143]. It has been thought for many years that acute pain and chronic pain are distinct processes involving different pain systems: the medial system with chronic pain and lateral system with acute pain [27,144]. So far, there is little evidence from functional neuroimaging studies that acute pain and chronic pain are processed within different parts of the pain matrix [80,145]. Neuroimaging studies in patients with peripheral or central nerve lesions have also implicated similar brain structures activated during experimental acute pain. Peripheral nerve lesions (compression, nerve section, or amputation) often lead to spontaneous neuropathic pain in the involved area. Imaging studies have demonstrated a decrease in regional cerebral blood flow in the contralateral thalamus [146] in patients with neuropathic pain. Interestingly, deep brain stimulation of the contralateral thalamus in patients with neuropathic pain has been shown to provide symptomatic relief [147] with accompanying increase in regional cerebral blood flow in this area as well as in the S1 and insular cortex. Additionally, changes in the somatotopy of the S1 have been shown to occur in amputees and have correlated with their experience of phantom pain [148]; similar findings have been found in CLBP patients [149]. Recently, comparisons between a small number of patients with CRPS and CLBP and normal subjects were made [150]. Significant changes in activation of the PFC were noted in the CRPS patients and those with CLBP, and each group had a relatively unique activation pattern. The patients with CRPS had a pattern that was more frontal and lateralized compared with the patients with CLBP, in whom the pattern demonstrated prefrontal activity that was extended to the anterior pole of the prefrontal cortex. The response of normal controls to thermal pain demonstrated a PFC activation pattern that was bilateral and primarily located at the junction between the insular cortex and inferior frontal gyrus. The authors concluded that CRPS and CLBP each demonstrated a unique activation signature, representing reorganization of cortical structures resulting in different cognitive and affective experiences of pain.

Magnetic resonance spectroscopy (MRS) makes it possible to investigate tissue metabolism and biochemistry directly [151]. Recent investigations have demonstrated differences in N-acetyl aspartate concentration in patients with CLBP compared with controls, anxiety levels (high versus low), and brain regions (dorsolateral PFC [DLPFC], OFC, thalamus, and cingulate), resulting in a three-way interaction [82]. There was a precise relation between perception and brain chemistry in that sensory versus affective component of pain was represented best in the DLPFC and OFC in CLBP patients. High versus low anxiety was represented in the OFC in normal subjects, and all four regions in CLBP patients, and the affective component of pain represented with improvements in the cingulate. It is expected that with increase in the spatial and temporal resolution and, number of substances, this technique will become more prevalent on its own or in combination with other neuroimaging techniques.

The neuroimaging of brain activity in patients with chronic pain is still in its infancy. The preliminary data support the notion that persistent chronic pain states involve functional abnormalities in the cortical and subcortical areas activated by noxious experimental stimuli in normal subjects.

Ablative and neuromodulatory targets for pain

Recently, neurosurgeons have used fMRI to evaluate brain function to identify boundaries and regions to determine losses expected from excising brain lobes in seizure disorders. It is expected that similar imaging techniques will be used in the

future to guide neurosurgical ablative procedures aimed at treating chronic intractable pain. In this situation, pain processing and perceptual areas will be mapped before excision. This may help to improve the efficacy of procedures like cingulotomy for chronic pain while reducing deficits of focused and sustained attention as well as the mild executive dysfunction seen in some patients [152,153].

Although ablative therapies are used only for truly intractable cases, neuromodulation is becoming a more commonly used treatment for chronic pain. Motor cortex and deep brain stimulation have been used successfully for the treatment of chronic pain conditions. Recently, fMRI was used to provide frameless image-guided electrode placement for motor cortex stimulation of patients with chronic phantom limb pain [154,155]. It is anticipated that the use of neuroimaging techniques will expand to identify further targets for electrode placement.

Drug development and assessment

Combining neuroimaging with pharmacologic studies is an excellent marriage of two complementary disciplines. Drugs may have an impact on brain activity by causing changes in baseline levels, or they may modulate brain activity resulting from an experimental stimulus. Opioids, which work by binding to μ receptors, have been the drug most studied using neuroimaging techniques. They exert their effect through multiple mechanisms, including reducing nociceptive signals reaching the CNS [156,157], activating descending modulatory analgesic systems (eg, PAG) [158], and modulating the affective component of pain through activity in the ACC and amygdala [118,119]. The effect of opioids on limbic region brain activation during painful stimuli was recently shown to have a significant gender difference, supporting the notion that men and women respond differently to this class of medication [159].

Opioids are excellent drugs to investigate the reward and analgesic circuits in the brain. Neuroimaging studies investigating reward have demonstrated that distinct reward circuitry can be distinguished from pain networks. Reward regions include the nucleus accumbens (NAc), ventral tegmentum/periaqueductal gray (VT/PAG), sublenticular extended amygdala of the basal forebrain (SLEA), and orbital gyrus (Gob) [160,161]. Morphine has been found to activate classic pain as well as reward circuits.

PET studies have yielded similar results when investigating CNS activity related to opioid infusions [119,120,162]. One distinct advantage of PET over fMRI in drug assessment is the ability to perform specific ligand-binding studies. Recent studies using a labeled version of the μ agonists carfentanil or diprenorphine, combined with PET imaging, were able to look directly at opioid binding in brain [145,163]. These ligand-binding studies demonstrated similar results to the drug infusion studies.

Ligands for other pharmacologic classes are being developed and will soon be used in pain studies. Additionally, ligands probing the serotonergic, adenosinergic, and dopaminergic systems have already been developed for PET studies and should provide further knowledge about the role these neurotransmitters have in acute and chronic pain.

The implications of pharmacologic neuroimaging studies for understanding pain and future treatments for chronic pain are significant. Investigating the plastic changes thought to occur in the reward and pain circuitry as a result of chronic pain should help us to understand the mood and behavioral alterations (eg, depression, anxiety) in our chronic pain patients better [164,165]. Furthermore, chronic opioid therapy is becoming more accepted for chronic nonmalignant pain and is associated with a small but real risk of addiction. The hypothesized abnormalities in brain reward circuitry occurring in chronic pain may play a role in the pain patient who becomes addicted. This will be the basis for future studies investigating CNS responses to opioids in chronic pain patients and addicts.

Treatment efficacy

Functional neuroimaging can be used to characterize the central abnormalities in chronic pain and eventually may be used to track treatment efficacy. There are few studies that have initiated this attempt to use neuroimaging in the assessment of spinal and brain neuromodulation for pain relief. Many include somatosensory evoked potentials (SEPs) and nociceptive spinal (RIII) reflexes, and a few have used PET [166], which have been applied to investigate the mechanisms and to optimize the application of neurostimulation procedures. PET has recently been used to demonstrate changes in cerebral blood flow during motor cortex stimulation for pain control. PET studies highlight the thalamus as the key

structure mediating functional motor cortex stimulation effects. Thalamic activation would trigger a cascade of synaptic events influencing activity in other pain-related structures, including the ACC, insular cortex, and upper brain stem. The use of functional neuroimaging in combination with clinical electrophysiology may provide insight into the mechanisms of action of interventions, guide clinical decision making, and contribute to optimize patient selection for a given intervention.

Future functional neuroimaging studies of pain in human beings

Recent advances in functional neuroimaging promise to provide unprecedented opportunities to explore the neural mechanisms underlying pain, linking decades of research in animal models to clinical practice. Although the field of functional neuroimaging is coming of age, there are still many obstacles to overcome. Many key regions that are known to be part of the pain matrix are subcortical regions or at the spinal cord level. They may involve small volumes that may be difficult to investigate with current functional neuroimaging technology because of what is being measured (eg, fMRI measures blood oxygenation and flow, EEG measures extracellular current, MEG measures intracellular current). Furthermore, there are significant limitations in spatial resolution (eg, PET, MRS) and in source localization (eg, EEG, MEG). Studies using multimodal imaging may help to overcome this issue. In addition to spatial and temporal functional information, studies of anatomic and functional connectivity may prove useful in the converging evidence of the neural circuitry involved in pain perception and how cognitive and affective factors modulate pain. For example, diffusion tensor imaging (DTI) provides microscopic structural information of oriented tissue in vivo noninvasively. White matter tract structure measured by water proton nonrandom anisotropic diffusion is highly sensitive to subtle changes and is finding utility in studies of cognition and various disorders [167]. Although studies of functional connectivity can be studied using fMRI, EEG, and MEG issues related to signal detection and statistical inference remain [168,169]. In addition, imaging techniques like MEG are a valuable tool to measure the temporal relation between brain regions. PET and MRS are also valuable in identifying the metabolism and specific neurotransmitters involved in pain processing. Further, techniques like transcranial magnetic stimulation (TMS) may be used to identify the causal relation between pain perception and certain brain regions thought to be involved in the perception of pain [169–174] and to measure corticospinal excitability [175–181] as has already been studied extensively in various neurologic and psychiatric disorders [182]. The advent of real-time fMRI is another exciting tool that may be useful in the studies of pain [183]. Recently, we have begun to study chronic pain patients and healthy individuals by externally applying pain to examine how one can learn to modulate the perception of pain using feedback of fMRI BOLD signals of brain regions related to pain in real time [184,185]. This technique not only provides causal evidence between certain brain regions and the perception of pain but may have therapeutic potential. Finally, another interesting development in this field is the combination of functional neuroimaging and genetics [186]. Functional neuroimaging, because of its unique ability to assay information processing at the level of brain within individuals, provides a powerful approach to explore the genetic basis of individual differences in complex behaviors and vulnerability to various disorders. Because it is known that responses to pain and other stressors are regulated by interactions between multiple brain areas and neurochemical systems, in one recent study, researchers examined the influence of a common functional genetic polymorphism affecting the metabolism of catecholamines on the modulation of responses to sustained pain in human beings [187]. They found that the COMT *val158met* polymorphism was related to the human experience of pain and concluded that this may underlie interindividual differences in the adaptation and responses to pain and other stressful stimuli. These directions are likely to shape our understanding of pain perception further and may be useful in assessing or developing new or existing treatments.

Summary

Pain remains a serious health care problem affecting millions of individuals, costing billions of dollars, and causing an immeasurable amount of human suffering. In designing improved therapies, there is still much to learn about peripheral nociceptor, nerves, and the spinal cord, and brain stem modulatory systems. Nevertheless, it is the brain that presents us with an incredible opportunity to understand the experience we call pain.

Functional neuroimaging is helping to unlock the secrets of the sensory and emotional components of pain and its autonomic responses. These techniques are helping us to understand that pain is not a static disease with the pathologic findings localized to the periphery but is instead a highly plastic condition affecting multiple central neural systems. Functional neuroimaging is transforming our understanding of the neurobiology of pain and will be instrumental in helping us to design more rational treatments ultimately aimed at reducing the impact of pain on our patients. It is opening windows into the function of the brain that were previously closed.

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