Chapter 13

Imaging Pain

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OBJECTIFYING THE PAIN EXPERIENCE

Over the past 15 years, we have witnessed a shift in our understanding of pain processing in humans from the peripheral nervous system to the central nervous system (CNS). Concurrent developments in methodologies that allow us to "image" brain activation in response to neuronal firing have enabled us to make this shift; we can readily and noninvasively determine the neuroanatomic substrate of pain perception in humans. Objectifying this subjective phenomenon has been the goal of pain researchers for decades, for obvious reasons. Slapping the cry baby at school and doing the same to a Tibetan monk would leave one sobbing but the other not so much as blinking. But is one really "feeling more pain" than the other at a physiologic level, or is it more a question of tolerance levels, coping, and attention, as well as individual past and present circumstances? The extent of tissue damage (or nociception) does not necessarily correlate with the amount of pain experienced for either of the subjects in the example, and neither do the behavioral changes measured (volume of vocalization, grimacing, limping, and so on). This nonlinear relationship between nociception and pain is not a novel concept; however, it does confound our ability to diagnose, prioritize, and treat pain patients. Pain is a conscious experience, an interpretation of the nociceptive input influenced by memories, and emotional, attentional, and cognitive factors. Pain is therefore a subjective experience. The International Association for the Study of Pain (1994) uses the following to define pain (53): "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

This definition encapsulates the problem for researchers, physicians, therapists, care workers, and families who deal with pain patients. Pain is more than simple tissue damage and the brain has a central role to play in generating each individual's pain experience. Clearly it would be useful to measure the levels of pain in patients objectively and reliably. It is not yet clear whether brain imaging methods provide an unequivocal level of objectivity. However, recent evidence supports their increasing utility in not only providing a noninvasive "assay" of nociception and, subsequently, pain perception, but also information about how central influences, such as sensitization/plasticity, attention, distraction, anxiety, depression, and other cognitive changes can impact the incoming nociceptive drive to produce an altered pain perception. Here, we review the field of pain imaging from the somatic and visceral pain fields and give specific examples of how these methodologies have contributed to our understanding of pain perception, its measurement and its modulation via behavioral and pharmacologic interventions.

BRAIN IMAGING AND THE NEUROANATOMY OF HUMAN PAIN PROCESSING

Functional brain imaging methods have revolutionized our understanding of how the human brain works, exploding onto the fields of neuroscience and medicine giving us unprecedented opportunities to "see" the brain in action (38,48,88). Pain research has benefited enormously from these developments; however, to better understand this literature it is useful to consider what aspects of brain activity we are measuring. Figure 13-1A displays the physiologic correlates of brain electrical activity. There is considerable evidence that local cerebral blood flow (CBF) changes reflect variations in local synaptic activity, as measured using positron emission tomography (PET) (75). The blood oxygenation level–dependent (BOLD) signal, detected using functional magnetic resonance imaging (fMRI) reflects simultaneously changes in local CBF and variations in deoxyhemoglobin (72). More recently, the neurophysiologic basis of the BOLD response has been further investigated and the findings confirm that the BOLD contrast mechanism reflects the input and intracortical processing of a

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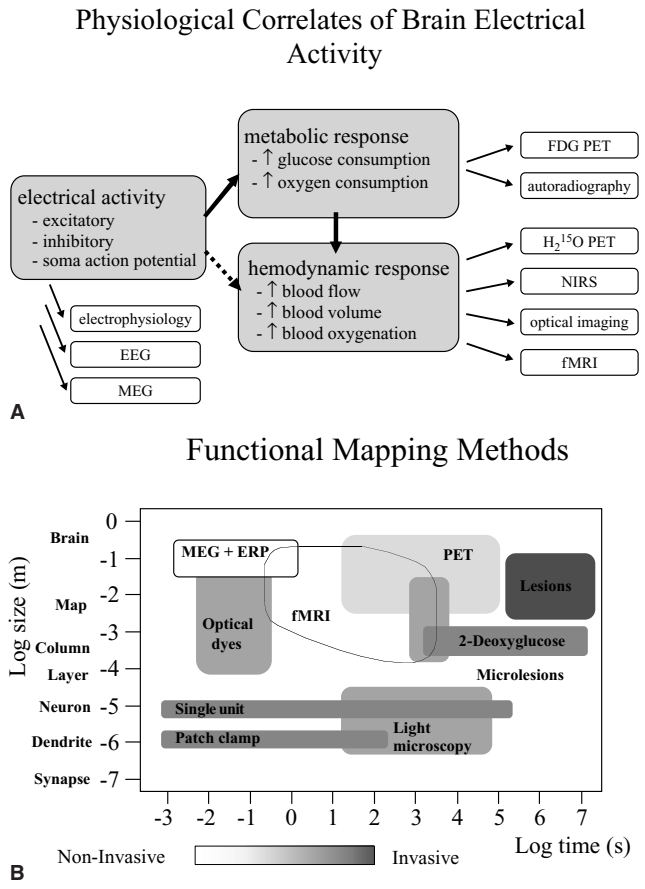

FIGURE 13-1. **(A)** Schematic showing the physiologic basis of what the major imaging methodologies measure during brain activation studies. Several methods exist that directly measure the electrical activity that occurs with synaptic activity and activation; these are electroencephalography (EEG), magnetoencephalography (MEG), and direct electrophysiologic recording using electrodes. In response to the neuronal electrical activity, there is an increased metabolic response required to support the prior electrical activity, and several methods allow one to measure this aspect of neuronal activation, namely, fluro-deoxy-glucose positron emission tomography (FDG-PET) and autoradiography. Finally, to provide the oxygen and glucose needed for this increased metabolism, cerebral blood flow (CBF), blood volume (CBV) and blood oxygenation must increase, and H_2O^{15} PET, near-infra-red spectroscopy, optical imaging, and fMRI measure these changes. **(B)** Schematic displaying key factors to be taken into consideration when performing a brain imaging experiment: spatial and temporal resolution as they relate to degree of invasiveness.

given area (44). Figure 13-1B displays how three other factors interact across these common brain imaging methods. In essence, you have a trade off between invasiveness and spatial/temporal resolution. It is clear from Figure 13-1B that fMRI scores reasonably well both spatially and temporally, and in addition is completely noninvasive. The noninvasive aspect of fMRI enables longitudinal studies to be performed safely, where patients can be followed and imaged several times during the course of their disease progression or therapeutic intervention. fMRI thus allows a broad range of sophisticated cognitive and neurophysiologic experiments to be performed, expanding our knowledge of brain function enormously and extending the early PET literature. A review of this material along with the pros and cons of PET versus fMRI is beyond the scope of this chapter; however, there are several excellent reviews and books that cover the basic principles, methods, and scientific contributions that fMRI and PET have made to neuroscience (24,38,48,49,63,77,88).

Most modern medical textbooks still claim that nociceptive signals arrive from the periphery via the spinal cord to the thalamus where they are distributed to sensory cortices, which process these signals to generate the conscious perception of pain. If pain imaging has contributed anything to the literature it is to dispel this myth. Summarizing the many excellent meta-analyses and reviews of the pain imaging literature that now exist (9,14,30,41,58,63), we can produce a more realistic diagram that highlights the key brain regions involved in processing nociceptive inputs to generate the conscious perception of pain in humans. This "pain matrix," as it is often described, is shown in Figure 13-2. It should be remembered that the list of cortical regions is not extensive and how these regions interconnect to relay information and influence processing in specific brain regions is still being determined. The key to successful pain imaging is to dissect the multidimensionality of pain into dissociable brain regions that can then be targets for therapeutic intervention.

Varying combinations of factors (nerve damage, inflammation, hyperalgesia, anticipation, anxiety, fear, depression, etc.) within patients obviously lead to observable differences in clinical pain profiles, abilities to cope, and possibly the differences seen in treatment outcomes. Brain imaging can help us to "see" and thereby determine the extent to which each of these factors contribute to the patient's pain providing useful information to guide diagnoses and appropriate treatment.

Albe-Fessard et al. (1) and Melzack (51) coined the idea that a neuromatrix for pain processing exists that comprises at least two main human nociceptive systems working in parallel: the medial and lateral pain systems. For many years a division of function within these pathways was asserted in that the lateral pathway processed the sensory-discriminatory aspects of pain experience and included structures such as the ventroposteriorlateral nucleus of the thalamus and sensory cortices, whereas the medial pathway processed the affective–cognitive–motivational aspects of pain processing and included structures such as the ventrocaudal part of the medial dorsal nucleus, anterior cingulate cortex, amygdala, and other limbic structures. It would appear, however, from various pain imaging experiments on both normal controls and increasingly in patients that this simple division of function between these parallel systems is not adequate

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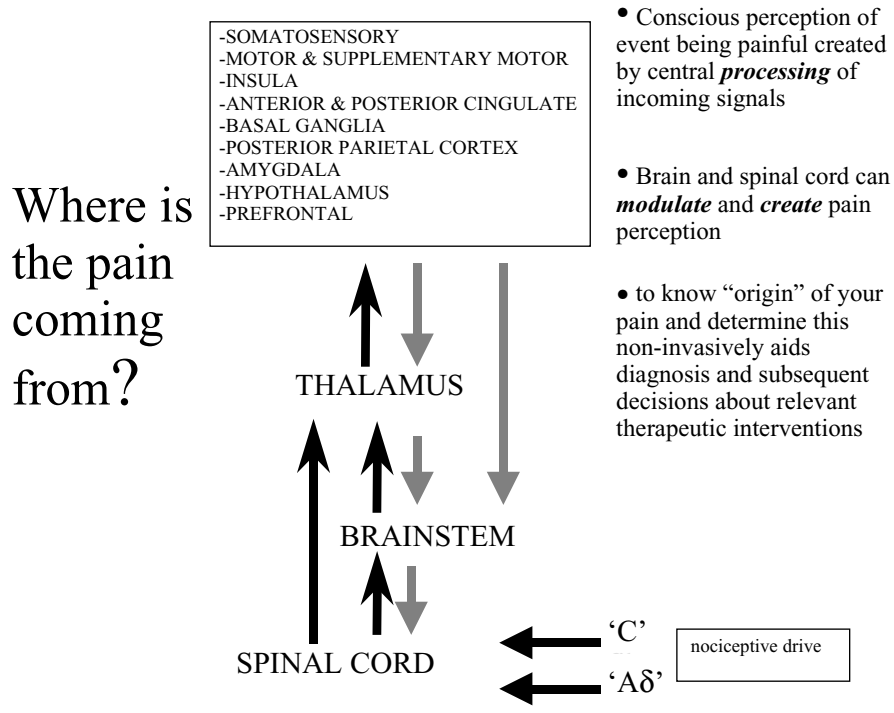

FIGURE 13-2. Realistic schematic of nociceptive pathways from the periphery to supraspinal regions.

to explain all our findings. In a review, Price (67) puts forward a schematic, largely based on pain imaging data, that attempts to label specific brain regions with specific aspects of the pain experience from an acute nociceptive event toward the development of chronicity, during which the affective dimension becomes dominant. In this scenario, a nociceptive input first drives arousal, autonomic, and somatomotor responses that largely recruit the reticular formation of the brainstem, hypothalamus, supplementary motor area, and amygdala, but in addition there is an awareness of nociceptive sensations processed by the sensory cortices, posterior parietal complex, and insula cortex. Subsequent to this nociceptive sensation there is an assessment of perceived intrusion or threat that is most likely processed by the posterior parietal complex and insula cortex but influenced by the arousal and autonomic responses. There is then an immediate pain unpleasantness that is likely generated by the anterior cingulate cortex followed by second-order appraisals processed within prefrontal cortex with secondary pain affects manifest as the situation becomes chronic. This is an appealing framework that nicely fits with many imaging experiments; however, it does not take into account those situations where there is a top-down dysfunction that either generates or exacerbates pain perception. An alternative proposal for viewing pain has recently been proposed by Craig (12) that encourages us to think about pain as a homeostatic emotion rather than pain and temperature being an aspect of touch. Only time and further pain imaging experiments will confirm or refute this new concept for understanding pain processing, but it highlights how recent imaging data combined with conventional neurophysiologic measurements can provoke new ideas and hypotheses.

EXPERIMENTAL EVIDENCE

How reliable a "marker" of the subjective pain experience is the brain signal as measured by PET or fMRI? Confidence in the technique as an objective readout of the pain experience is only possible if this is true.

Coghill and colleagues (11) performed a study that examined pain intensity processing within the human brain using PET. In their study, they combined psychophysical assessment of graded nociceptive stimuli with PET to identify a brain network that perhaps subserved the processing of one dimension of the pain experience, namely, pain intensity. Multiple regression analysis revealed statistically reliable relationships between perceived pain intensity and activation of a functionally diverse group of brain regions, including those known to be important in sensation, motor control, affect, and attention. Pain intensity–related activation occurred bilaterally in the cerebellum, putamen, thalamus, insula, anterior cingulate cortex, and secondary somatosensory cortex, contralaterally in the primary somatosensory cortex and supplementary motor area, and ipsilaterally in the ventral premotor area. The authors conclude that their results confirm the existence of a highly distributed, bilateral brain mechanism engaged in the processing of pain intensity. They also conclude that the

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conservation of pain intensity information across multiple, functionally distinct brain areas contrasts with the traditional view that sensory-discriminative processing of pain is confined within the somatosensory cortex, and perhaps accounts for the preservation of conscious awareness of pain intensity after extensive cerebral cortical lesions. Similar parametric studies have been done by others (7,18), which support the notion that brain activation, as detected with imaging methods, is a reliable readout of the subjective perception. Coghill et al. recently expanded this concept to address the issue that some individuals claim to be "sensitive" to pain, whereas others claim they tolerate pain well (10). Because it is difficult to determine whether these subjective reports reflect true interindividual differences in the experience, Coghill et al. combined psychophysical ratings to define pain report and "sensitivity" with fMRI to assess brain activity in 17 normal, healthy subjects. They found that highly "sensitive" individuals exhibited more frequent and more robust pain-induced activation of the primary somatosensory cortex, anterior cingulate cortex, and prefrontal cortex than did less "sensitive" individuals. For normal healthy controls, this study validates the subjective report as a reliable indicator of what is going on within the brain. However, in patients this might not be the case and divergence might exist between the report and the brain activation pattern because of the complexity of other factors that might contribute.

The studies described teach us primarily about pain intensity; however, to disentangle components such as anticipation, fear, anxiety, attention/hypervigilance, or even depression first requires the development of novel cognitive and pharmacologic paradigms, initially applied to normal subjects in an experimental pain imaging laboratory. In our laboratory we have performed several such studies, some of which are discussed later (2,3,36,37,45,64-66,71,74,78–83,91,92). More recent work has focused on examining the neural correlate of gender differences in pain perception and pain coping with the use of brain imaging (19,54). Differences have been observed both in terms of pain report and functional brain activation in several different brain regions, but a clear account of what regions are consistently differently activated and why requires further studies and investigation.

Other data from the laboratory of Borsook et al., and relevant to the field of headaches, has focused on determining the somatotopic activation in the human trigeminal pain pathways. They used fMRI to image pain-associated activity in three levels of the neuraxis: the medullary dorsal horn, thalamus, and primary somatosensory cortex by applying noxious thermal stimuli to facial skin at sites within the three divisions of the trigeminal nerve (V1, V2, and V3). Significant activation was observed in the ipsilateral spinal trigeminal nucleus within the medulla and lower pons in response to at least one of the three facial stimuli. In addition, activation from the three facial stimulation sites exhibited a somatotopic organization along the longitudinal (rostrocaudal) axis of the brainstem that was consistent with the classically described "onion skin" pattern of sensory deficits observed in patients after trigeminal tractotomy. Activation in the primary somatosensory cortex displayed a laminar sequence that resembled the trigeminal nucleus, with V2 more rostral, V1 caudal, and V3 medial. These findings were developed in a further study where the same authors determined the specific and somatotopic fMRI activation in the trigeminal ganglion by brush and noxious heat stimulation of the face within the receptive fields of each of the three divisions of the trigeminal nerve in controls. For both stimulus types, activation was somatotopically organized within the ipsilateral ganglion, as predicted by the known anatomic segregation of the neurons comprising the ophthalmic (V1), maxillary (V2), and mandibular (V3) divisions of the nerve. Signal decreased after brush stimuli and increased after the application of noxious heat. The abilities to detect somatotopic activation within the ganglion and to segregate non-noxious mechanical from noxious thermal stimuli suggest that fMRI will be valuable for measuring changes in the trigeminal ganglion in various clinical pain conditions (6,13).

Modulation of the Pain Experience

Descending Systems

Just as pain signals are important for survival, it is as important to regulate pain signaling in the nervous system. Head and Holmes postulated very early the existence of a descending pain modulatory system (28). Later this postulation was empirically confirmed (27) and provided a theoretical framework with the gate-control theory of Melzack and Wall (52). Wall also demonstrated a tonic regulatory influence from the brainstem on the spinal cord dorsal root level (87). The concept of the descending analgesic system was further developed when Mayer and Price demonstrated that stimulation in the periaqueductal gray matter produced analgesia without any concurrent effects on alertness or motor performance, so-called stimulus-produced analgesia (47). In the periaqueductal grey (PAG), ascending pain stimuli are integrated with descending influences from the diencephalon and the limbic forebrain. Important regions are the hypothalamus, the amygdala, the rostral components of the anterior cingulate cortex, insula, and the orbitofrontal cortex. PAG also receives influence from nearby nuclei of the catecholaminergic tone setting systems. Interestingly, microinjections of opioids into the amygdala produce analgesia, and analgesia that can be blocked by interference locally in the PAG (29). The PAG has strong bidirectional connections to the rostral medulla and this could be viewed as part of the pain modulation process given the role of the medulla in autonomic control. There are also strong suggestions that the analgesic

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system is heavily related to the endogenous opioid systems (96).

The relationship between reported pain intensity and the peripheral stimulus that evokes it depends on many factors, such as the level of arousal, attention, and expectation or anticipation. These factors are in the process of being characterized on the physiologic and pharmacologic levels by means of functional imaging (2,3,36,37,45,64–66,71,74,78–83,91,92). These "psychological" factors are in turn regulated by overt and covert information as well as more general contextual cues that establish the significance of the stimulus and help to determine an appropriate response. Simple manipulations with attention alter the subjective pain experience as well as the corresponding pattern of activation during a pain stimulus (3,45,61).

The study of pain modulation is challenging because it is best observed in awake humans or possibly in freely moving animals (22,55). However, most experimental conditions preclude important aspects of pain modulation, namely the issue of subjective control. The knowledge that it is possible to leave the pain experiment at any time is in itself a very marked deviance from the clinical situation. Often the main reported reason for suffering that is reported by the patient is the inability to control the pain. In most pain imaging experiments, the regulatory systems are not evident, but if potent pain stimuli are used, it results in the activation of the hypothalamus and the PAG region (32). Curiously, Ingvar et al. did not note any activation in the PAG and brainstem in a study of provoked cluster headache (31) and attributed this to the nontraumatic type of pain that was evoked. The activity in the brainstem descending system entails dynamic properties with initial high activity that decreases following a period of habituation (62). It is possible to manipulate the activity in this region by cognitively based contextual manipulations. Telling a subject that an upcoming painful event will be short or long has bearing on the top-down regulation. The pain system is differentially activated during the initial stages of the pain stimulus based on the knowledge of how long the stimulus duration will be. If longer endurance is required under the contextual constraints of the experimental situation coping mechanisms are instigated. This leads to a concurrent downregulation of the activity in the amygdala (57). Earlier pain imaging work has also shown the relevance of top-down cognitive control via the PAG-rostral ventromedial medulla (RVM) inhibitory system on pain perception in humans. Using high-resolution fMRI Tracey et al. (82) showed that activation within the periaqueductal gray was significantly increased during a distraction condition and that the total increase in activation was predictive of changes in perceived intensity. In addition, the relationship between the subjective behavioral report and the objective PAG activation change, as measured with fMRI, was significantly correlated. These results are displayed in Figure 13-3. Extrapolating these findings to the wider public, and the observation that some patients cope and deal with their pain better than others, it could be there is a physiologic basis for this observation, which is linked to a dysfunction of the descending pain modulatory system. It should not be forgotten that the descending pain modulatory system can also facilitate nociceptive events at the dorsal horn of the spinal cord (25), and thereby contribute to an amplification of the nociceptive drive. Our understanding of this role in the generation of chronic pain is rapidly growing, and indeed recent data from our laboratory directly support structures within this pathway in the generation and maintenance of secondary hyperalgesia, a key feature of neuropathic pain (97). It remains to be seen what role such brainstem structures play via the facilitatory route in the generation and maintenance of headaches but recent human brain imaging experiments by Welch et al. are highlighting its relevance (8,89) and clearly brain imaging will play a major role in the elucidation of the structures involved (80,81).

The role that hypervigilance, distraction, and attention have on descending brainstem pathways as well as placebo influences via a "top-down" mechanism are only recently being realized with the use of pain imaging experiments (60,86). Rainville discusses in a recent review the possibility that activity within the human anterior cingulate cortex and other classical limbic structures that are closely related to the subjective experience of pain unpleasantness may reflect the regulation of endogenous mechanisms of pain modulation (68).

Indeed, a recent study has shown that distraction modulates connectivity of the cingulofrontal cortex and the midbrain during pain, as detected using fMRI (84). Examining whether the placebo response harnesses these brain networks also, Petrovic et al. used PET and confirmed that both opioid and placebo analgesia share a common neuronal network and are associated with increased activity in the rostral anterior cingulate cortex (rACC). They also observed a covariation between the activity in the rACC and the brainstem during both opioid and placebo analgesia, but not during the pain-only condition (60). The key findings from this study are shown in Figure 13-4. A more recent study by Wager et al. has extended these results and examined placebo-induced changes in fMRI signals during the anticipation and experience of pain (86). Because the experience of pain arises from both physiological and psychological factors that include one's beliefs and expectations, placebo treatments that have no intrinsic pharmacologic effects could produce analgesia by altering expectations. Wager et al. found that placebo analgesia was related to decreased brain activity in pain-sensitive brain regions, including the thalamus, insula, and anterior cingulate cortex, but was also associated with increased activity during anticipation of pain in the prefrontal cortex. Their findings suggest a potential mechanism

Imaging Attentional Modulation of Pain in the Periaqueductal Gray in Humans

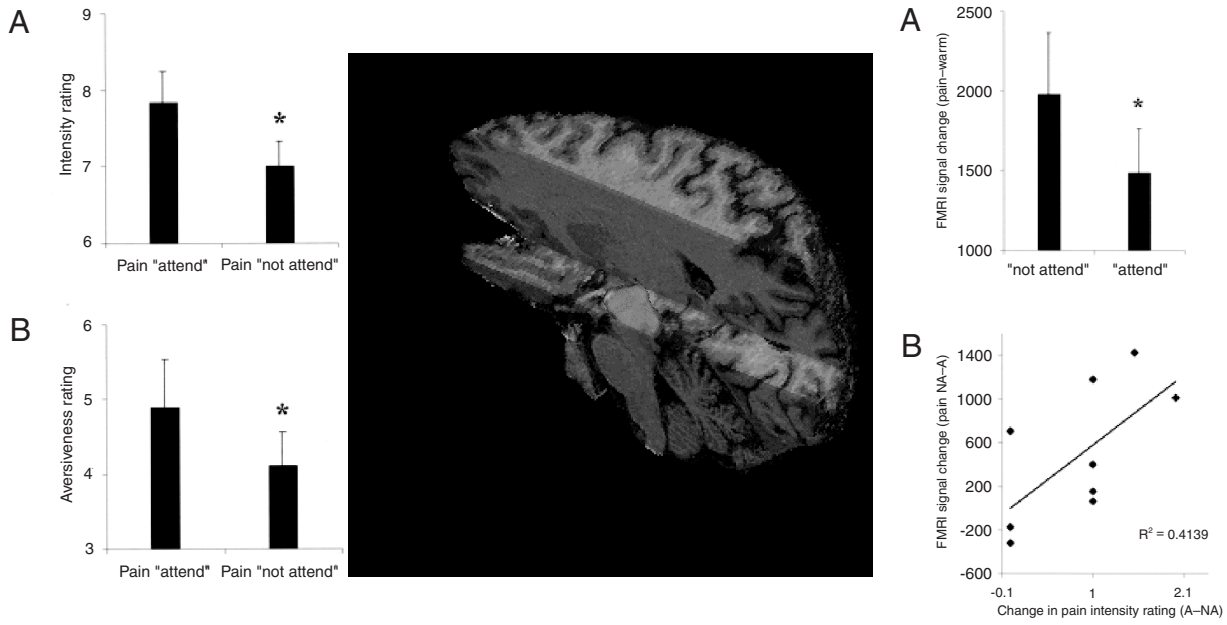

FIGURE 13-3. Representative fMRI activation within the periaqueductal gray in response to noxious heat (middle figure). Left-hand figure **(A, B)**. Graphs showing the pain scores (mean ± SE) between conditions for intensity **(A)** and aversiveness **(B)** (*p <0.05). Right-hand figure **(A, B)**. Total signal intensity (arbitrary units) within the periaqueductal gray for the two attentional conditions **(A)** (mean ± SE; *p <0.05). **(B)** Correlation of total signal intensity change within the periaqueductal gray and total change in pain intensity between the two conditions was significant (p <0.025). Data represented taken from Tracey I, Ploghaus A, Gati JS, et al. Imaging attentional modulation of pain in the periaqueductal gray in humans. *J Neurosci.* 2002;22:2748–2752).

of placebo action; the representation of expectations within regions of the prefrontal cortex that modulate activity in pain-responsive areas. Further experiments to examine the opioid system and its effects on pain processing have been performed in the laboratory of Tracey et al. (78,91,92). In addition, Borsook et al. recently examined the effects of a μ-opioid antagonist, naloxone, on the endogenous opioid systems and the CNS response to mild noxious heat during its infusion. Cortical activation was induced in regions including cingulate, prefrontal cortex, and insula for naloxone versus saline infusion. Subcortical regions showing increased signal change included hippocampus and entorhinal cortex. A 46°C-stimulus delivered to the back of the hand induced an overall increase in activation in a number of regions in the naloxone group that were not seen in the saline group (e.g., insula, orbitofrontal cortex, thalamus, and hippocampus). These results show that naloxone, even in the absence of psychophysical effects, produces activation in several brain regions that are known to have high levels of mu-opioid receptors and may be involved in endogenous analgesia. Earlier fMRI work by the same group showed that noxious thermal stimuli (46°C) produce significant signal change in putative reward circuitry of the brain as well as in classic pain circuitry (4,5), highlighting yet further the complexity of neuronal networks involved in pain processing and its modulation.

Anticipation, Anxiety, and Attentional Influences on Pain Perception

The knowledge of the nature of an upcoming pain is itself a potent regulator of the pain experience. In all pain experiments there is always a first time when the pain stimulus is given, a time when the only information at hand is that given by the experimental leader about the pain stimulus. Already the second stimulus is influenced heavily by the first pain experience. So although the first stimulus activates, for example, the caudal portion of anterior cingulate cortex, a well-known stimulus

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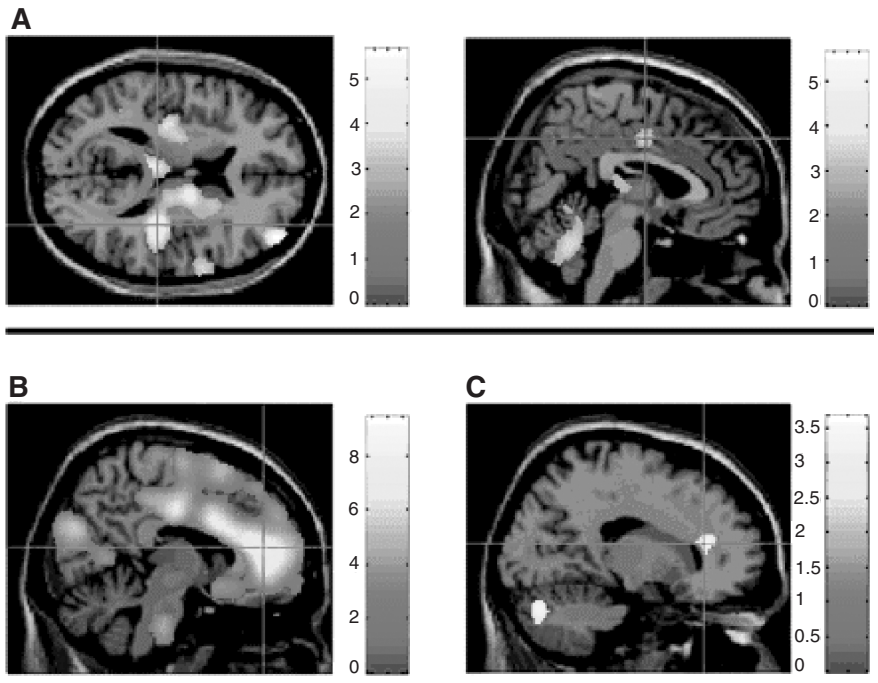

FIGURE 13-4. **(A)** Increased activity was observed in the right (cross) and left insula (left panel, horizontal section), in the thalamus (left panel), and in the caudal ACC (right panel, sagittal section) during the main effect of pain. **(B)** The activation was most pronounced in the rACC during the main effect of opioids. Increased activity is apparent in the lower pons. **(C)** Increased activity in the same area of the rACC was also seen in the placebo effect during pain. Reproduced with permission from Petrovic P, Kalso E, Petersson KM, et al. Placebo and opioid analgesia-imaging a shared neuronal network. *Science.* 2002;295:1737–1740.

tends to deactivate this region, at least in the preparatory phase (33). This illustrates the importance of the anterior cingulate cortex (ACC) in the pain processing in addition to its role in attention, working memory regulation, motivation, and executive processes (20). It is perhaps obvious that pain and its anticipation have separate adaptive consequences, such as pain motivating escape and the anticipation of pain allowing future painful events to be avoided. However, it also has separate maladaptive consequences in that anticipation of pain in itself can provoke excessive anxiety and fear, thereby making it an important factor in chronic pain. Ploghaus et al. used fMRI in normal healthy subjects to dissect the experience of acute experimental pain into its anticipation and pain itself by imaging the neural correlates underlying each experience (66). Colored lights signaled in advance the two kinds of thermal stimulation and subjects learned during the imaging session which color signaled pain and which signaled warmth. The high temporal resolution of fMRI was ideally suited to this paradigm, and this was exploited to identify brain regions involved in the experience of pain itself by comparing brain activation during pain with activation during warm stimulation. In addition, brain regions involved in the anticipation of pain were identified by comparing brain activation during the colored light preceding pain to activation during the colored light preceding warm stimulation.

The results from this comparison showed for the first time that pain and its anticipation have separable neural components that are both spatially and temporally dissociable across three brain regions. This provides two targets for therapeutic intervention or perhaps a target for the noninvasive monitoring of cognitive behavioral therapies aimed at alleviating the more attentive/anticipatory component of a patient's pain. In addition, the signal changes from these brain regions highlight that as the subject learns the association between pain and its anticipation, the brain signal in the anticipatory region increases—supporting the idea that brain imaging, particularly fMRI, can be used for both spatial mapping of brain activation as well as a temporal tool to investigate learning effects in the brain. An extension of this work aimed to modulate the anxiety levels of normal healthy subjects to prove that the pain report need not be related to the nociceptive drive when central processing confounds exist (such as being in an anxious state) (64). It is common clinical experience that anxiety about pain can exacerbate the sensation (50,76). To investigate this in an experimental setting on control subjects one can increase the pain physiologically by turning up the heat, and psychologically by increasing the pain-related anxiety. In this study, the neural mechanism by which anxiety causes an increased pain perception were examined and contrasted with the process by which enhanced nociceptive stimulation (turn the heat up) increases pain (64). Figure 13-5 displays the key findings: an increased pain perception owing to anxiety-related changes does not have the same brain activation pattern as an increased pain perception owing to an increased nociceptive drive with the entorhinal complex and hippocampal formation playing a key role in anxiety-provoked pain exacerbation. Recent novel imaging studies have highlighted the ability of brain imaging to show us the neural basis of everyday unpleasant experiences, such as feeling emotionally or socially hurt and excluded, or empathizing

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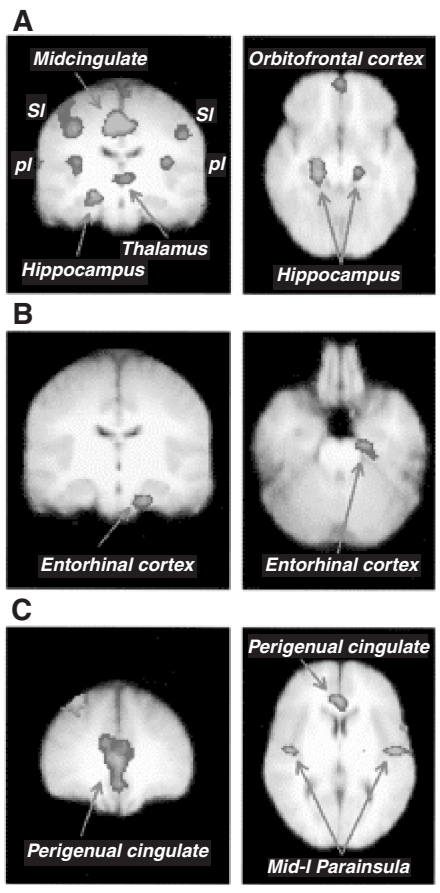
A: Heat intensity-related changes in pain intensity

B: Anxiety-related changes in pain intensity

C: Brain regions whose activity significantly correlates with changes found in B



Separate circuits allow separate targets

FIGURE 13-5. **(A)** Temperature-related activation increases in perceived pain (HT/HA versus LT/HA): Bilateral S1, dorsal margin of posterior insula, thalamus, midcingulate, and right hippocampus. **(B)** Anxiety-related activation increases in perceived pain (LT/HA versus LT/LA) associated with significant activation in left entorhinal cortex. **(C)** Also found areas in perigenual cingulate, mid-/para-insula that had activity significantly correlated with entorhinal fMRI signal during pain modulation by anxiety (LT/HA and LT/LA). Reproduced with permission from Ploghaus A, Narain C, Beckmann CF, et al. Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci.* 2001;21:9896–9903.

with the patient's pain and suffering. In all these situations, various pain matrix structures are accessed and activated without a concomitant nociceptive input and a perception of pain is produced (23,34,73).

Several PET and fMRI studies have also shown that pain processing can be modulated by cognitive mechanisms (3,45,56,59,69,70,90). Rainville et al. used hypnotic suggestion to modulate the perception of unpleasantness during noxious stimulation. When the subjects were suggested to perceive the noxious stimulation as highly unpleasant there was a concomitant increase in the activity in the ACC significantly more than when the subjects were suggested to perceive the same stimulation as less unpleasant (69). However, the activity in the somatosensory areas was unaltered. Because lesion studies and animal studies have indicated that the ACC is involved in processing pain unpleasantness, this finding indicates that cognitive mechanisms may specifically modulate specific substrates of the pain network (85). Petrovic et al. used a different approach to show that pain networks may be modulated by cognitive demands (61). Most people are aware that pain perception can decrease and even disappear when one is engaged in a distracting task. They tested this mechanism by involving the subjects in a highly attention demanding task during noxious stimulation and were able to show that when subjects solved the maze task and a painful stimulation was induced, they perceived less pain as compared with when there was no competition for attentional space. At a neural level, activity was significantly attenuated in somatosensory regions and the PAG in this condition. Recently, further work has also shown that cognitive distraction attenuates the pain-evoked activity in the ACC, insula, and the thalamus (3,45).

All the regions discussed are involved in pain processing, and modulation in their activity coincides with the changes in pain perception reported; however, the cortical structures that drive these pain matrix modulations are less easy to identify, but most likely involve the lateral orbitofrontal region and rostral ACC (58).

IMAGING CLINICAL PAIN: THE TWENTY-FIRST CENTURY CHALLENGE

This is the challenge for the twenty-first century, bringing together what we have learned using experimental pain in normal healthy controls to a better understanding of the more complex situation in a real patient. A first goal is

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GRBT050-13 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:43

simply to use brain and spinal cord imaging as a simple readout of their pain, as discussed. Studies to image activations within the human spinal cord are in their infancy (43), but are vital if we are to specifically localize areas of central sensitization to either spinal or supraspinal sites. Returning to the issue of clinical pain, it has often been thought that acute and chronic pain are very distinct processes, possibly with specific types of chronic pain processed within discreet brain regions. However, if you examine chronic pain, many types such as arthritic pain are a mixture of recurrent acute and chronic pain. Also, it makes no sense to process each type of pain in a separate and discrete nociceptive system; this would be wasteful. Indeed there is little evidence from the few clinical imaging studies to date for a division of function within the pain matrix on the basis of acute or chronic when using experimental pain in patients compared to controls (15–17,39,40). A more useful approach might be to image their clinical pain, as opposed to an exogenously delivered painful stimulus. The results to date suggest that for most types of pain, including visceral, there are not specific brain areas dedicated to specific types of pain and the pain matrix is largely activated as seen in experimental pain (31,42), although the data are sparse at this stage and further work combined with more sophisticated ways of measuring different aspects of processing within the pain matrix is needed. Examining a patient's ongoing pain is more difficult with brain imaging, particularly fMRI that requires some modulation of activity from baseline for the signal to be detectable. A few early PET studies were able to image ongoing pain in neuropathic patients and found a trend toward decreased activity within the thalamus (35); however, confirmation of this result will only come from further studies on relevant patient groups.

A recent study by Gracely et al. highlights a more fruitful approach to unraveling the brains response to clinical pain (26). They examined pain catastrophizing and neural responses to pain among persons with fibromyalgia. Because catastrophizing has been suggested to augment pain perception through enhanced attention to painful stimuli and heightened emotional responses to pain, they hypothesized that catastrophizing would be positively associated with activation in structures believed to be involved in these aspects of pain processing. Their findings suggest that pain catastrophizing, independent of the influence of depression, is significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal ACC, dorsolateral prefrontal cortex), emotional aspects of pain (claustrum, closely connected to amygdala), and motor control. Their results support the hypothesis that catastrophizing influences pain perception by altering attention and anticipation, and heightening emotional responses to pain. The second approach to understanding clinical pain is to use human models of chronic pain and recent work combining pain imaging with these models is underway (21,46,93–95,97); however, these studies are in their infancy and their utility yet to be fully validated.

CONCLUSION

Pain imaging, despite being a relatively new field, has made significant contributions to our understanding of somatic and visceral pain processing in humans in terms of the neural correlates of pain perception. Extrapolation of these developments and knowledge to the field of headaches is in its infancy, but we can look forward to a similar advancement of our understanding in the years ahead.

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GRBT050-13 Olesen- 2057G GRBT050-Olesen-v6.cls August 1, 2005 16:43

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