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Review

The Cerebral Signature for Pain Perception and Its Modulation

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Clinical pain is a serious public health issue. Treatment of pain-related suffering requires knowledge of how pain signals are initially interpreted and subsequently transmitted and perpetuated. This review article is one of three reviews in this issue of Neuron *that address our understanding of the pain process and possible solutions to the problem from both cellular- and systems-level viewpoints.*

Our understanding of the neural correlates of pain perception in humans has increased significantly since the advent of neuroimaging. Relating neural activity changes to the varied pain experiences has led to an increased awareness of how factors (e.g., cognition, emotion, context, injury) can separately influence pain perception. Tying this body of knowledge in humans to work in animal models of pain provides an opportunity to determine common features that reliably contribute to pain perception and its modulation. One key system that underpins the ability to change pain intensity is the brainstem's descending modulatory network with its pro- and antinociceptive components. We discuss not only the latest data describing the cerebral signature of pain and its modulation in humans, but also suggest that the brainstem plays a pivotal role in gating the degree of nociceptive transmission so that the resultant pain experienced is appropriate for the particular situation of the individual.

Pain as a Major Medical Health Problem

Pain that persists for more than three months is defined as chronic and as such is one of largest medical health problems in the developed world. It affects approximately 20% of the adult population, particularly women and the elderly (Breivik et al., 2006). While the management and treatment of acute pain is reasonably good, the needs of chronic pain sufferers are largely unmet, creating an enormous emotional and financial burden to sufferers, carers, and society. Per annum, it is estimated that the cost of chronic pain to Europe is E200 billion and to the USA over $150 billion. Improvements in our ability to diagnose chronic pain and develop new treatments are desperately needed but to achieve this we need robust and less subjective "readouts" of the pain experience.

Innovative methods, like molecular and systems neuroimaging, that can assess changes within the central nervous system (CNS) of patients and relate these findings to the wealth of information from animal studies, have great potential and promise. Indeed, improvements in our ability to identify the extent of changes within the CNS, due to chronic pain, in animals and humans have strengthened the case for considering chronic pain as a disease in its own right. The mechanisms that contribute to the generation and maintenance of a chronic pain state are increasingly investigated and better understood. A consequent shift in mindset that treats chronic pain as a disease rather than a symptom is accelerating advances in this field considerably.

Tying this new body of knowledge from patients and normals with the extensive animal data on pain processing in the CNS is timely. Common aspects regarding how pain perception is mediated and modulated are being identified; this is the focus of our review.

Pain as a Perception

Pain is a conscious experience, an interpretation of the nociceptive input influenced by memories, emotional, pathological, genetic, and cognitive factors. Resultant pain is not necessarily related linearly to the nociceptive drive or input; neither is it solely for vital protective functions. This is especially true in the chronic pain state. Furthermore, the behavioral response by a subject to a painful event is modified according to what is appropriate or possible in any particular situation. Pain is, therefore, a highly subjective experience, as illustrated by the definition given from the International Association for the Study of Pain (Merksey and Bogduk, 1994): "an unpleasant sensory and emotional experience associated with actual or

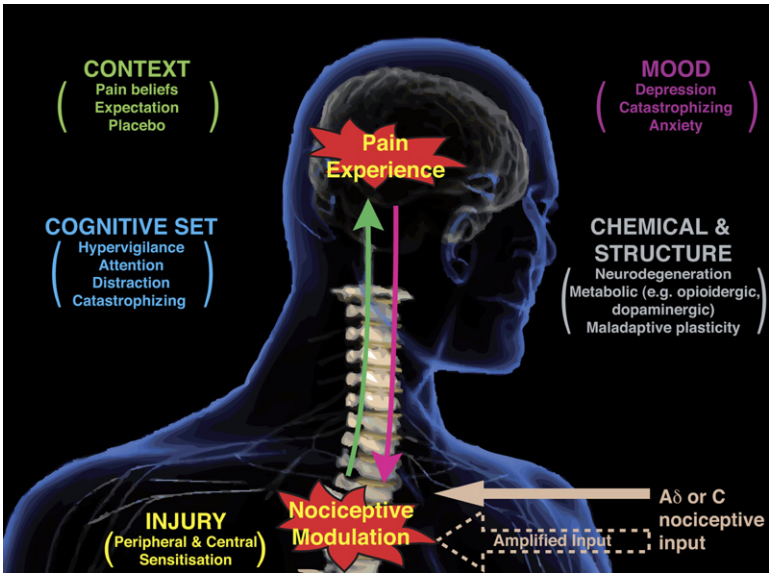

Figure 1. Schematic Illustrating the Main Factors that Influence Nociceptive Inputs to Affect Pain Perception

potential tissue damage, or described in terms of such damage.''

By its very nature, pain is therefore difficult to assess, investigate, manage, and treat. Figure 1 illustrates the mixture of factors that we know influence nociceptive inputs to amplify, attenuate, and color the pain experience. We know also from more recent data how a painful experience can occur without a primary nociceptive input (Derbyshire et al., 2004; Eisenberger et al., 2003; Raij et al., 2005; Singer et al., 2004), further complicating the story but perhaps providing an alternative explanation for how pain might arise in difficult clinical cases where the organic cause is not obvious. What is clear is that many factors influencing pain percepts are centrally mediated, and our ability to unravel and neuroanatomically dissect their contribution has only been feasible since neuroimaging tools allowed us noninvasive access to the human CNS. Determining the balance between peripheral versus central influences and ascertaining which are due to pathological versus emotional or cognitive influences will clearly aid decisions regarding the targeting of treatments (i.e., pharmacological, surgical, cognitive behavioral or physical rehabilitation). Understanding how complex behavioral influences such as anxiety, depression, belief states, and cognition change the pain experience in animals is difficult to assess due to the lack of sophisticated behavioral paradigms and overdependence on threshold or withdraw measures. However, a greater emphasis is now being placed on measures of spontaneous pain behaviors as well as on developing and utilizing animal models of pain that more clearly mirror specific chronic human pain conditions (Blackburn-Munro, 2004; Lindsay et al., 2005; Schwei et al., 1999). Additionally, animal pain models now routinely take into consideration the genetic background, age, gender, and stress levels of the animal as these have been shown to potentially have a significant impact on the pain phenotype observed in animals as well as humans (Boccalon et al., 2006; Craft et al., 2004; Mogil, 1999; Mogil et al., 1997, 2006). Indeed, a more integrated approach for translating knowledge bidirectionally between human and animal studies is already proving beneficial, as recently demonstrated in the unexpected identification of the potential central role of GTP cyclohydrolase (GCH1), the rate-limiting enzyme for tetrahydrobiopterin (BH4) synthesis, as a key modulator of peripheral neuropathic and inflammatory pain in animal models and humans suffering chronic pain (Tegeder et al., 2006).

Basic Neuroanatomy of Central Pain Processing and the "Cerebral Signature" for Pain Perception

Beyond the peripheral nociceptor and dorsal horn, nociceptive information ascends to the thalamus in the contralateral spinothalamic tract (STT) and to the medulla and brainstem via a spinoreticular (spinoparabrachial) and spinomesencephalic tracts. These tracts serve different purposes related to both their lamina origin in the dorsal horn and final central destination (Dostrovsky and Craig, 2006). Spinal projections to the brainstem are particularly important for integrating nociceptive activity with homeostatic, arousal, and autonomic processes, as well as providing a means to indirectly convey nociceptive information to forebrain regions after brainstem processing. The capacity for projections to the brainstem to directly influence *both* spinal and forebrain activity clearly suggest these pathways play a direct role in affecting the pain experience; data from animals, healthy subjects, and patients increasingly confirm the central role that the brainstem plays in mediating changes in pain perception.

Functional and anatomical divisions of the thalamus, the main relay site for nociceptive inputs to cortical and subcortical structures, have been made on the basis of their connections to specific spinal cord laminae in various animal species and in humans (Craig, 2003b; Pralong et al., 2004). Lamina I STT neurons largely project to the

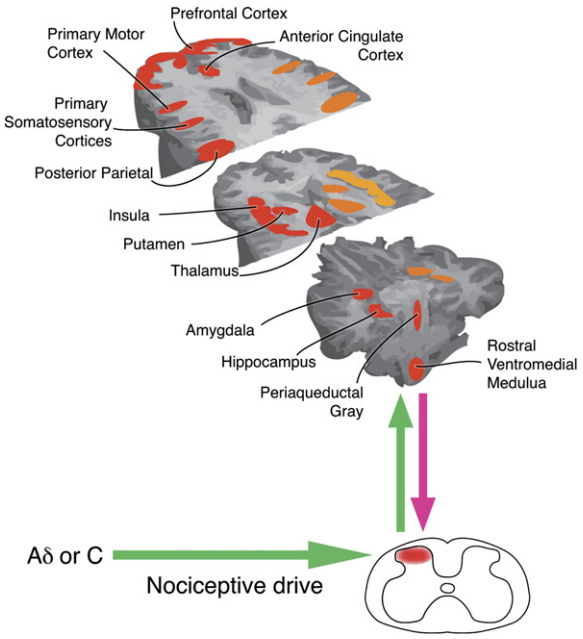

Figure 2. Neuroanatomy of Pain Processing
Main brain regions that activate during a painful experience, highlighted as bilaterally active but with increased activation on the contralateral hemisphere (orange).

ventral posterior nucleus (VP), the posterior part of the ventral medial nucleus (VMpo), the ventral posterior inferior nucleus (VPI), and the ventral caudal division of the medial dorsal nucleus (MDvc). Recent evidence, however, questions the lamina I STT projection to VP (Craig, 2006). Lamina V STT axons terminate in VP, VPI, ventral lateral nucleus, and intralaminar nuclei. However, the thalamus and its connections spinally and supraspinally are still debated in terms of nociceptive processing in humans. Nevertheless, higher-resolution imaging studies coupled to surgical investigations in humans have confirmed the relevance of nuclei identified to date from animal studies (Montes et al., 2005; Romanelli et al., 2004; Seghier et al., 2005). As a critical relay site, it's perhaps not surprising that the thalamus is implicated in chronic pain. Decreased thalamic blood flow contralateral to the site of pain in patients with cancer has been shown (Di Piero et al., 1991), and in patients developing pain following lesions to the peripheral or central nervous system, thalamic hypoperfusion occurs. Of course, such hypoperfusion could reflect either a decrease in neural activity or deafferentation. A recent study of a patient with a left medullary infarct (Wallenberg's syndrome) attempted to distinguish between these possibilities (Garcia-Larrea et al., 2006). In this patient, extensive right-sided sensory deficits were accompanied by left-sided facial pain, and a PET scan revealed that the reduction of blood flow occurred in the right thalamus, contralateral to the area of pain. The repeat scan following pain relief afforded by motor cortex stimulation showed restoration of thalamic perfusion. This suggests that thalamic hypoperfusion indeed reflects the pain state, although it may not be pathophysiological per se. Future areas of investigation should include targeted deep-brain stimulation in patients, informed by white matter diffusion tractrography connectivity maps, to better determine the role of specific thalamic nuclei in pain perception and its modulation.

The Pain Matrix

Because pain is a complex, multifactorial subjective experience, a large distributed brain network is subsequently accessed during nociceptive processing. Melzack (1999) first described this as the pain "neuromatrix," but it's now more commonly referred to as the "pain matrix"; simplistically it can be thought of as having lateral (sensory-discriminatory) and medial (affective-cognitive-evaluative) neuroanatomical components (Albe-Fessard et al., 1985). However, because different brain regions play a more or less active role depending upon the precise interplay of the factors involved in influencing pain perception (e.g., cognition, mood, injury, and so forth), what comprises the pain matrix is not unequivocally defined, and the literature is not always consistent regarding what regions are to be included. In our opinion, for the pain matrix to retain its utility, it needs to be viewed not as a stand-alone entity but rather as a substrate that is significantly and actively modulated by a variety of brain regions, and it is this interaction that in large part determines the pain experience.

A recent meta-analysis of human data from positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) studies does provide clarity regarding the commonest regions found active during an acute pain experience (Apkarian et al., 2005). These areas include: primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices as well as the thalamus (Figure 2). That is not to say these areas are the fundamental core network of human nociceptive processing (and if ablated would cure all pain), although recent studies investigating pharmacologically induced analgesia do show predominant effects in these brain regions (Casey et al., 2000; Geha et al., 2007; Rogers et al., 2004; Wagner et al., 2007; Wise et al., 2002, 2004). Other regions such as basal ganglia, cerebellum, amygdala, hippocampus, and areas within the parietal and temporal cortices can also be active dependent upon the particular set of circumstances for that individual (Figure 2). Perhaps we need to move toward an individualized neural "pain signature" rather than forcing this complex, subjective experience into the constraints of a rigid neuroanatomical pain matrix (Tracey, 2005b). This is especially true when considering the neural representation of chronic, ongoing, or spontaneous pain in patients, something that has been studied only recently and appears to not be represented necessarily by the conventional pain matrix concept (Baliki et al., 2006). And of course data showing activity of the near entire pain matrix without a nociceptive input during hypnosis and empathy manipulations support the notion it is time to reconsider how we

define central pain processing with respect to the origin of the input and resultant perception and meaning (Craig et al., 1996; Derbyshire et al., 2004; Raij et al., 2005; Rainville et al., 1997; Singer et al., 2004). That is not to say pain experienced without a nociceptive input (sometimes referred to as psychogenic pain) is any less real than "physically" defined pain; indeed, neuroimaging studies have highlighted the physiological reality of such experiences due to the extensive neural activation that occurs. Rather, it is to say we do not yet have a central signature that unequivocally reflects peripheral nociceptive inputs. Studies using laser-evoked potentials (LEPs) and MEG that focus more specifically on temporal aspects of nociceptive processing, within spatially less well-defined brain regions, provide signals reflecting the exogenous components (i.e., fast direct nociceptive input represented by the operculoinsula and/or S2 region) and endogenous components (i.e., later integrated and convolved signal represented by the ACC) (Bentley et al., 2004; Garcia-Larrea et al., 2003; Hobson et al., 2005; Iannetti et al., 2005a; Ohara et al., 2004a). Great emphasis has, therefore, been given to either the spatial *or* the temporal representation of nociceptive processing within functionally defined brain regions, without consideration for how their activation in concert causes a perception of pain. Pain perception, similar to many complex experiences, emerges from the flow and integration of information among specific brain areas; greater emphasis on understanding temporal integration among these spatially defined brain regions is needed and human multimodal imaging as well as animal studies may provide the solution.

In part, the focus on the rather simplified pain matrix is a casualty of the intense focus and success pain researchers have had in understanding molecular and cell biology of primary afferent sensory neurons and their interactions in the spinal cord (Julius and Basbaum, 2001; Mantyh et al., 2002; Morris et al., 2004; Woolf and Salter, 2000). Over the past 20 years, this success has resulted in a large scale "migration" of pain researchers studying the involvement of higher centers of the brain (cerebral cortex, thalamus, amygdala) to focusing on the sensory neuron and spinal cord. However, with the advent and success of noninvasive neuroimaging techniques in humans, greater emphasis in animal experiments must be now placed on how sensory neurons, the spinal cord, and higher centers of the brain act in concert if we are to truly begin to grasp how pain is perceived at a systems level. Combining data from human imaging studies with neuroimaging, cellular, molecular, and behavioral studies in animals has the potential to make similar progress in understanding how higher centers of the brain are involved pain perception as has been made in understanding the neurobiology of primary afferent nociceptors.

Interrelationship between Nociception and Pain Perception: A Pivotal Role for the Brainstem

To understand at a system and molecular level how nociceptive inputs are processed and altered to subsequently influence changes in the pain experienced, it is useful to separately examine the main factors known to alter pain perception.

Cognition and Context

Attention

Anecdotal and experimental observations provide strong evidence that attention is effective in modulating the sensory and affective aspects of the pain experience (Levine et al., 1982; Miron et al., 1989; Villemure and Bushnell, 2002). FMRI and neurophysiology studies show attention- and distraction-related modulations of nociceptive-driven activations in many parts of the brain's pain processing regions, with concomittant changes in perception (Bantick et al., 2002; Legrain et al., 2002; Ohara et al., 2004b, 2004c; Petrovic et al., 2000; Peyron et al., 1999). However, it is not known if a specific cerebral network dedicated to the modulation of pain by attention exists and if so, if it is different to the network that produces analgesia in other circumstances (i.e., during placebo, acupuncture [Napadow et al., 2007], or pharmacological manipulation). One candidate network that might elicit pain modulation in a generalized fashion is the descending pain modulatory system; another network specific perhaps to attention could further recruit other brain regions involved in pain perception.

The Descending Pain Modulatory System

The descending pain modulatory system is a well-characterized anatomical network that enables us to regulate nociceptive processing (largely within the dorsal horn) in various circumstances to produce either facilitation (pronociception) or inhibition (antinociception) (Fields, 2005; Hagbarth and Kerr, 1954). The pain-inhibiting circuitry, of which the periaqueductal gray (PAG) is a part, is best known and contributes to environmental (e.g., during the fight-or-flight response) and opiate analgesia (Fields, 2005). There are descending pathways that facilitate pain transmission, however, and it is thought that sustained activation of these circuits may underlie some states of chronic pain (see later; Gebhart, 2004; Porreca et al., 2002; Suzuki et al., 2004). Knowledge regarding this critically important system largely came from animal studies. Early work repeatedly demonstrated that spinal cord excitability was directly influenced by descending inputs originating in higher centers of the brain and that this descending modulation could be inhibitory and/or facilitatory in nature (Basbaum and Fields, 1984; Porreca et al., 2002; Ren and Dubner, 2002). The ability of higher centers of the brain to modulate the transmission of nociceptive information in the CNS was demonstrated in the early 1900s by Sherrington who showed that nociceptive reflexes were enhanced following spinal cord transection (Sherrington, 1906). Over the last several decades, evidence has accumulated that a variety of brain regions are involved in this descending modulation and include the frontal lobe, anterior cingulate cortex (ACC), insula, amygdala, hypothalamus, PAG, nucleus cuneiformis (NCF), and rostral ventromedial medulla (RVM). Figure 3 illustrates the

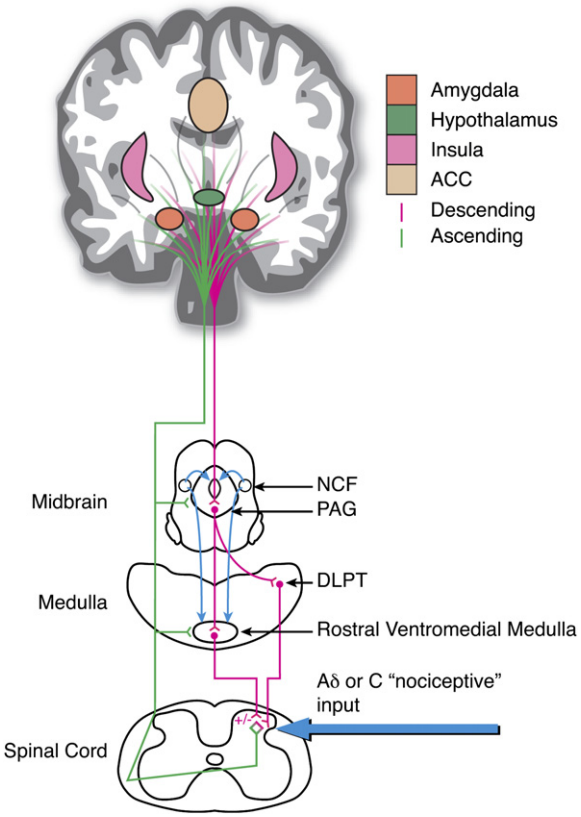

Figure 3. The Descending Pain Modulatory System
NCF (nucleus cuneiformis); PAG (periaqueductal gray); DLPT (dorsolateral pontine tegmentum); ACC (anterior cingulated cortex); +/– indicates both pro- and anti- nociceptive influences, respectively.

key anatomical features of the descending pain modulatory system.

More recently, researchers have investigated whether alteration in people's attention influences brainstem activity and, therefore, nociceptive processing via these corticobrainstem influences. In an early study using high-resolution imaging of the human brainstem, we showed significantly increased activity within the PAG in subjects who were distracted compared to when they paid attention to their pain, with concomitant changes in pain ratings. Indeed, the change in pain rating between attending and distracting conditions correlated with the change in PAG activity across the group, suggesting a varying capacity to engage the descending inhibitory system in normal individuals (Tracey et al., 2002). Further work using a counting stroop cognitive task attempted to identify the cortical structures involved in mediating this brainstem influence and subsequent change in pain matrix activity to produce behavioral analgesia (Bantick et al., 2002). Valet and coworkers extended the work further by using connectivity analysis, an advanced method of analyzing functional imaging, on FMRI data collected from controls receiving nociceptive stimulation while performing a similar distraction/cognitive task. They showed that the cingulofrontal cortex exerts top-down influences on the PAG and posterior thalamus to gate pain modulation during distraction (Valet et al., 2004). These studies provide clear evidence for the involvement of brainstem structures in the attentional modulation of pain perception, and recent work using diffusion tractrography confirms that anatomical connections exist between cortical and brainstem regions in the human brain, thereby enabling such top-down influences (Hadjipavlou et al., 2006). Adventurous studies examining how biofeedback aids both a normal subject's or a chronic pain patient's capacity to modulate their pain experience, using real-time FMRI data analysis procedures, provide novel ways to help us better understand the cortical regions involved in the attentional control of pain, enabling novel treatment options (deCharms et al., 2005). A clinical feature of many chronic pain patients is "hypervigilance" to pain and pain-related information. This has a direct impact not only on their resultant pain perception but also quality of life if it impacts cognitive performance. There are a number of explanations for this attentional effect that are often the target for interventions such as cognitive behavioral therapies (Crombez et al., 2005). Clearly, recognizing the central role of the brainstem in helping to mediate the analgesia and focusing efforts to strengthen cortical connectivities to structures such as the PAG will be important in future work and treatment developments.

Context

The commonest route to understand how context can influence pain perception is via a placebo manipulation. Much of our knowledge of the placebo effect has come from early animal studies based upon Pavlovian conditioning and expectancy (Benedetti et al., 2005; Haour, 2005). Recent work to translate these findings to humans has helped provide a systems framework by which the placebo effect and subsequent analgesia is mediated (Colloca and Benedetti, 2005; Price et al., 2006, 2007). Descending influences from the diencephalon, hypothalamus, amygdala, ACC, insular, and prefrontal cortex that elicit inhibition or facilitation of nociceptive transmission via brainstem structures are now thought to occur during placebo analgesia. Using PET, Petrovic and colleagues (2002) confirmed that both opioid and placebo analgesia are associated with increased activity in the rostral ACC, but they also observed a covariation between the activity in the rostral ACC and the brainstem during both opioid and placebo analgesia, but not during pain alone. Interestingly, high responders to placebo mirrored their ability to respond to real opioid injection compared to low placebo responders, possibly reflecting a genetic influence in mu-opioid receptors. Recently, Zubieta and colleagues (2005) confirmed that placebo analgesic effects are mediated by endogenous opioid activity on mu-opioid receptors using a molecular imaging approach in humans. Wager and colleagues (2004) extended these observations to consider whether or not placebo treatments produce analgesia by altering expectations. Using a conditioning design, Wager found that placebo analgesia was related to decreased

brain activity in classic pain-processing brain regions (thalamus, insula, and ACC) but was additionally associated with increased activity during anticipation of pain in the prefrontal cortex (PFC); an area involved in maintaining and updating internal representations of expectations. Stronger PFC activation during anticipation of pain was found to correlate with greater placebo-induced pain relief and reductions in neural activity within pain regions. Furthermore, placebo-increased activation of the PAG region was found during anticipation, the activity within which correlated significantly with dorsolateral PFC (DLPFC) activity. These results support the concept that prefrontal mechanisms can trigger opioid release within the brainstem during expectancy to influence the descending pain modulatory system and subsequently modulate pain perception. In a very recent experiment by Scott and colleagues, they examined the relationship between placebo-related expectations and dopamine release within the nucleus accumbens in humans using molecular imaging. They found that activation of dopamine release occurred during placebo administration and that the extent of release was related to anticipated effects as well as perception-anticipation mismatches and subsequent placebo development. Furthermore, using a reward task and fMRI, they found that expectancy of monetary gain increased nucleus accumbens activity proportionally to those measures obtained from the molecular imaging study in the same subjects (Scott et al., 2007). Studies such as these are significantly improving our understanding of the placebo effect as well as expectation of relief; areas of significant relevance for assessing treatment outcomes in clinical trials.

Emotions and Mood

For both chronic and acute pain sufferers, mood and emotional state has a significant impact on the resultant pain perception and ability to cope. For example, it is a common clinical and experimental observation that anticipating and being anxious about pain can exacerbate the pain experienced. Anticipating pain is highly adaptive; we all learn in early life to avoid hot pans on stoves and not to put your finger into a candle flame. However, for the chronic pain patient it becomes maladaptive and can lead to fear of movement, avoidance, anxiety, and so forth. Many studies aimed at understanding how anticipation and anxiety cause a heightened pain experience have been performed over the past decade (Hsieh et al., 1999; Ploghaus et al., 1999, 2000, 2001; Porro et al., 2002, 2003; Song et al., 2006). Critical regions involved in amplifying or exacerbating the pain experience include the entorhinal complex, amygdalae, anterior insula, and prefrontal cortices. More recently, we have found that the degree of anticipation to a pain event positively correlates with the reported pain intensity across a group of healthy individuals, and this amplification is mediated in part via activity within the ventral tegmentum area of the brainstem and entorhinal cortex, as well as the PAG (Fairhurst et al., 2007). This data obtained in humans correlates well with animal data in demonstrating that there is a clear interaction between pain, anxiety, and mobility. While the body of animal data is at times conflicting (anxiety can be pro- or antinociceptive depending on the models used and the endpoints assessed), what is clear is that the pain response of the animal is emotion-specific, i.e., higher centers of the brain in large part determine the behavioral response to the same noxious stimulus. What is largely lacking, however, is a cellular, molecular, and systems understanding of how distinct areas of the brain interact to cause a heightened or diminished pain experience and how prior ''memories of pain'' are stored so as to influence current and future experiences of pain. Incorporating our understanding of noradrenergic, serotonergic, opioidergic, and now dopaminergic function in acute and chronic pain processing from animal studies with the capacity to image some of these neurotransmitters via molecular imaging in humans and manipulate their levels with pharmacological agents will lead to rapid advances in our understanding of how complex moods influence pain experience.

Depressive disorders often accompany persistent pain. Central neuronal plasticity may underlie both conditions, further complicating our ability to dissect the components contributing to clinical pain disorders (Castren, 2005). Although the exact relationship between depression and pain is unknown, with debate regarding whether one condition leads to the other or if an underlying diathesis exists, studies have attempted to isolate brain regions, such as the amygdale, that may mediate their interaction (Neugebauer et al., 2004). In another fMRI study, Giesecke and colleagues (2005) showed that activation in amygdala and anterior insula differentiated patients with fibromyalgia with and without major depression; however, more studies that specifically address the interaction between pain and depression are needed if we are to resolve the neuroanatomical basis for the comorbidity.

Another negative cognitive and mood affect that impacts pain is catastrophizing. This construct incorporates magnification of pain-related symptoms, rumination about pain, feelings of helplessness, and pessimism about pain-related outcomes (Edwards et al., 2006), and it is defined as a set of negative emotional and cognitive processes (Sullivan et al., 2001). A study on fibromyalgia patients found that pain catastrophizing, independent of the influence of depression, was 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 (Gracely et al., 2004). Clearly, these results support the notion that catastrophizing influences pain perception through altering attention and anticipation, as well as heightening emotional responses to pain.

It is interesting to speculate whether activity in such ''emotional'' brain regions due to chronic pain impacts performance in tasks requiring emotional decision making. Apkarian and colleagues (2004a) showed that during the Iowa Gambling Task, a card game developed to study

emotional decision making, chronic pain patients displayed a specific cognitive deficit compared to controls, suggesting such an impact might exist in everyday life. Such experiments are hard to reproduce in animal studies; however, if we are to understand what neural systems mediate this potential disruption, more work is needed combining these more complex paradigms with neuroimaging techniques (Seymour et al., 2007).

Prefrontal, Frontal, and Insular Cortex in Chronic Pain

It is clear from these few studies described and others in the literature (Apkarian et al., 2001, 2005; Lorenz et al., 2003; Phillips et al., 2003; Witting et al., 2006), that rostral anterior insula and pronounced PFC activation are consistently found across clinical pain conditions, irrespective of underlying pathology. A recent meta-analysis by Schweinhardt and colleagues (2006) highlighted that clinical pain is located significantly more rostrally in the anterior insula than nociceptive pain in healthy volunteers, consistent perhaps with current theories regarding interoception and body awareness (Craig, 2003a; Craig et al., 2000; Critchley et al., 2004). Indeed, anterior insular activity is found not only during subjective feelings of pain, but is associated with anxiety, depression, irritable bowel syndrome, chronic fatigue, fibromyalgia, somatization, and fear. Paulus and Stein (2006) have recently proposed a role for the anterior insula in generating an altered interoceptive prediction signal in individuals prone to anxiety. In their model, an increased predictive signal of a prospective aversive body state (i.e., pain) triggers an increase in anxiety, worried thoughts, and avoidance behaviors, with possible pain amplification. This model certainly fits with current data.

We are only beginning to unravel the roles of specific prefrontal and frontal cortical regions in pain perception; from other areas of cognitive neuroscience we can postulate roles reflecting emotional, cognitive, and interoceptive components of pain conditions, as well as perhaps processing of negative emotions, response conflict, decision making, and appraisal of unfavorable personal outcomes for more medial FC, ventrolateral, and medial PFC (Dolan, 2002; Kalisch et al., 2006; Ridderinkhof et al., 2004; Rushworth et al., 2004, 2005, 2007; Sakagami and Pan, 2007). Baliki recently showed in chronic back pain patients increased activity in mPFC, including rostral ACC, during episodes of sustained high ongoing pain. Furthermore, the medial PFC activity was strongly related to the intensity of chronic back pain (Baliki et al., 2006). In other pain studies, connectivity analyses of functional imaging data have highlighted the relevance of frontal cortical regions in mediating or controlling the functional interactions among key nociceptive processing brain regions to subsequently produce changes in perceptual correlates of pain, independent of changes in nociceptive inputs (Eisenberger et al., 2003; Lorenz et al., 2002; Tracey, 2005a). A specific role for the lateral PFC as a ''pain control center'' has been put forward in a study of experimentally induced allodynia in healthy subjects (Lorenz et al., 2002). In this study, increased lateral PFC activation was related to decreased pain affect, supposedly by inhibiting the functional connectivity between medial thalamus and midbrain, thereby driving endogenous pain-inhibitory mechanisms. More recent studies looking at control and pain support these concepts. Wiech and colleagues manipulated the level of control healthy subjects had over their pain and produced changes in pain ratings dependent upon the control condition and the subject's internal locus of control. Using fMRI, they showed that the analgesic effect of perceived control relies on activation of right anterolateral PFC (Wiech et al., 2006). It is perhaps important to note that the prefrontal cortex (specifically the dorsolateral PFC) is a site of major neurodegeneration and potential cell death in chronic pain patients (Apkarian et al., 2004b). These unexpected findings suggest that severe chronic pain could be considered a neurodegenerative disorder that especially affects the PFC. This could in turn have consequent negative effects on the descending inhibitory system and contribute to their chronic pain state.

There is no doubt that the extent to which a stimulus (like pain) is identified as emotive and subsequently produces and regulates an affective or emotive state is dependent upon activity in many other regions such as the amygdala, insular, ventral striatum, ACC, and hippocampus, as well as the PFC (Phillips et al., 2003). However, it remains to be determined whether emotional and cognitive influences such as hypervigilance, catastrophizing, anxiety, or depression all mediate part of their recognized influence on pain perception in chronic pain sufferers via the descending pain modulatory system. Recent advances in our ability to image activity within the human brainstem (Dunckley et al., 2005; Tracey and Iannetti, 2006) and map white matter tracts within the human brain noninvasively using diffusion tensor imaging and tractography (Behrens et al., 2003; Johansen-Berg and Behrens, 2006; Le Bihan, 2003) are already contributing to a better understanding of the neuroanatomical connectivity among different cortical, subcortical, and brainstem regions and, therefore, the likelihood of finding a functional nociceptive link for these ''top-down'' influences (Hadjipavlou et al., 2006). It is known from animal studies that the anterior insula is connected to brainstem structures such as PAG, RVM, NCF, and parabrachial nucleus (Fields, 2005); this provides a mechanism to partly explain how emotions and mood might influence changes in pain intensity perception. Additionally, as several of the brainstem descending modulatory regions are either ascending homeostatic integration sites or descending autonomic premotor sites, it is perhaps feasible that a specific link exists between pain, homeostasis, and interoception. Changes in the affective and cognitive state might influence interoception to produce a bias in behavior and decisions that affect outcome and pain perception. Evidence is accumulating to support such concepts linking homeostasis and pain; a recent study has provided the first evidence that the vanilloid receptor, TRPV1 (a

cation channel that serves as a polymodal detector of pain producing stimuli like capsaicin, protons [pH < 5.7] and heat) is also tonically activated in vivo and as such is involved in body temperature regulation (Gavva et al., 2007). Another study examined whether estradiol changes in women influence pro- and antinociceptive mechanisms (Smith et al., 2006). They found convincing estrogen-associated variations in the activity of mu-opioid neurotransmission that correlated with individual ratings of the sensory and affective perceptions of the pain, as well as the subsequent recall of that experience. Molecular imaging studies like these not only illustrate how systemic biochemical changes influence behavior and perception, but also provide novel opportunities to translate research findings between animal models and humans.

Injury

Recently, changes within the descending pain modulatory network have been implicated in chronic pain and in functional pain disorders (Gebhart, 2004; Porreca et al., 2002; Suzuki et al., 2004; Tracey and Dunckley, 2004). Changes are defined in terms of patients having either a dysfunctional descending inhibitory system or an activated and enhanced descending facilitatory system. There has been convincing evidence revealed regarding the differential involvement of the PAG, RVM, parabrachial nucleus (PB), dorsal reticular nucleus, and NCF in the generation and maintenance of central sensitization states and hyperalgesia in both animal models and, for the first time in humans, a human model of secondary hyperalgesia (Zambreanu et al., 2005). This evidence has added to the literature and the general notion that these structures play an important role, in addition to the dorsal horn, in generating and maintaining central sensitization.

Recent clinical studies are further highlighting how dysfunction within this system can be sufficient to generate key symptoms of chronic pain. A study by Wilder-Smith and colleagues (2004) investigated whether patients with irritable bowel syndrome had hypersensitivity and pain upon distension due to abnormalities in endogenous pain inhibitory mechanisms; they found this to be the case for patients compared with controls. In a study of central post-stroke pain following an ischemic brainstem injury, patients were found to experience pain in the body side contralateral to their lesion. Furthermore, by studying the patients using PET and a radiolabeled opioid receptor agonist, Willoch and colleagues (2004) found dramatic reductions in opioid-receptor binding in several key nociceptive processing brain regions. These findings suggest that an imbalance of excitatory and inhibitory mechanisms contributes to either the generation or the modulation of a pain experience both in patients and in controls. Mayer and colleagues (2005) examined whether visceral hypersensitivity found in patients with IBS might arise as a consequence of aberrant top-down descending influences. In a PET study, they observed greater activation of limbic and paralimbic circuits during rectal distension in patients with IBS compared with control subjects or patients with quiescent ulcerative colitis. Functional connectivity analysis suggested a failure to activate the right lateral frontal cortex permits the inhibitory effects of limbic and paralimbic circuits on PAG activation, the consequence of which may be visceral hypersensitivity. The same group recently examined the longitudinal change in perceptual and brain activation response to visceral stimuli in IBS patients (Naliboff et al., 2006). Among several changes, they noted a decreased brainstem activity to both the anticipation and experience of rectal inflation after 12 months.

Changes within the descending pain modulatory network in chronic pain, in terms of patients having either a dysfunctional descending inhibitory system or an activated and enhanced descending facilitatory system, are clearly implicated in these and increasingly other studies (Edwards, 2005; Goadsby, 2007; Sandrini et al., 2006). Seifert and Maihofner recently performed an fMRI study in healthy subjects experiencing innocuous and noxious cold as well as menthol-induced cold allodynia. Comparing cold allodynia with equally intense cold pain conditions, they show increased activations in bilateral dorsolateral prefrontal cortices and brainstem during cold allodynia (Seifert and Maihofner, 2007); reflecting the specificity of brainstem activity for this chronic pain symptom. These findings are supported by another study using the capsaicin model of hyperalgesia showing brainstem activity specific to secondary hyperalgesia (Mainero et al., 2007), results that fit with a clinical study showing differential involvement of brainstem nuclei between affected and unaffected sides in chronic neuropathic pain patients (Becerra et al., 2006). Furthermore, recent pharmacological studies are showing that gold-standard agents used to treat key symptoms of neuropathic pain mediate their influence on brainstem structures (Iannetti et al., 2005b).

While activation of the descending inhibitory system is generally viewed as desirable, it also has the potential to mask a pain that would be useful in early diagnosis and treatment of a disease (Mantyh, 2006). Recently, a transgenic mouse that spontaneously develops pancreatic cancer was used to determine if the endogenous pain inhibitory system might be tonically active in masking early-stage pancreatic cancer pain (Sevcik et al., 2006). These mice, like humans with pancreatic cancer, usually only display spontaneous morphine-reversible visceral pain-related behaviors when the cancer is advanced, the tumor has metastasized to vital organs, and effective treatment or cure is no longer possible (Hawes et al., 2000). To test whether CNS pathways might be masking early-stage pancreatic cancer pain, mice that spontaneously develop pancreatic cancer received subcutaneous administration of the CNS penetrant opioid antagonists naloxone or naltrexone. Following administration of these opioid antagonists, mice with early pancreatic cancer, who before demonstrated no spontaneous pain behaviors, now displayed a robust visceral pain-related behaviors. Furthermore, the endogenous opiates that tonically inhibit pancreatic cancer pain appear to exert their actions in the

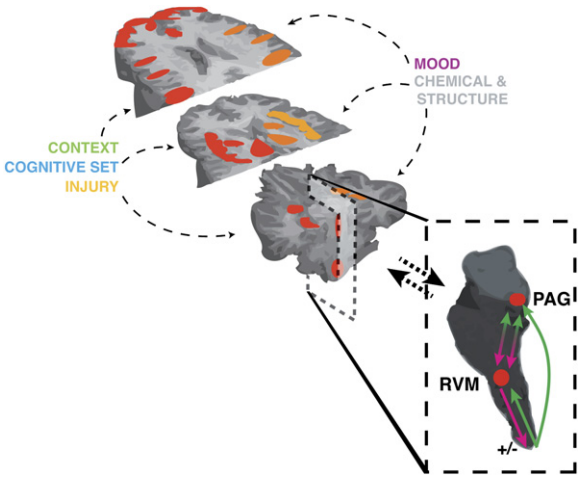

Figure 4. Current Hypothesis Regarding the Central Role of the Descending Pain Modulatory System during Different Pain Experiences

RVM (rostroventromedial medulla); PAG (periaqueductal gray); +/− indicates both pro- and anti- nociceptive influences, respectively.

CNS, as subcutaneous administration of the non-CNS penetrant opiate antagonist naloxone-methiodide did not induce visceral pain behaviors in early stage-mice, whereas intracerebroventricular injection of this same compound increased visceral pain behaviors. These data suggest that a CNS opiate-dependent mechanism tonically masks early-stage pancreatic cancer pain (Sevcik et al., 2006). What is impressive about these results is just how effectively the CNS can modulate pain. Once pancreatic cancer pain appears, in both humans and mice, it is frequently severe. This endogenous CNS inhibition of pain in pancreatic cancer is reminiscent of the impressive analgesia that was originally demonstrated by Reynolds in 1969, where it was shown that electrical stimulation of rat PAG in awake moving rats allowed abdominal surgery to be conducted without the use of general anesthesia (Reynolds, 1969).

Together, these and other studies reinforce the concept that CNS inhibitory or facilitatory mechanisms are remarkable in their efficacy in being able to amplify or decrease the pain experience (Vanegas and Schaible, 2004). Therefore, understanding which CNS areas are involved in engaging or disengaging this descending modulatory system has significant potential to not only further our understanding of how pain is perceived, but also in developing mechanism-based therapies for treating different types of acute and chronic pain. Figure 4 summarizes our current opinion regarding the central relevance of the brainstem and the descending modulatory system in affecting the pain experienced in varying circumstances.

Molecular Imaging and Metabolic Changes: Altered Opioidergic and Dopaminergic Pathways

The availability of PET ligands for opioid and dopamine receptors has allowed the study of these receptor systems in several clinical pain states, providing yet further evidence for an imbalance of excitatory and inhibitory mechanisms contributing to the generation or modulation of pain in patients. Early opioid ligand studies (Jones et al., 1994) showed decreased binding in patients with chronic pain that normalized after reduction of their pain symptoms. Regional differences in ligand binding have also been found in neuropathic pain studies (Jones et al., 1999, 2004; Willoch et al., 2004) with decreased binding in several key areas involved in pain perception. Future studies, in particular longitudinal studies that correlate binding potential with pain intensity, could help elucidate whether decreased receptor availability is caused by increased release of endogenous opioids or decreased receptor density. A study of restless legs syndrome showed that the opioid-binding potential is negatively correlated with the affective dimension of the McGill Pain Questionnaire (von Spiczak et al., 2005), suggesting a decrease of receptor density might be responsible for the increase in pain affect.

The dopaminergic pathways have also been implicated in pain processing in animal (Altier and Stewart, 1999; Schmidt et al., 2002) and patient studies (Ertas et al., 1998; Hagelberg et al., 2004; Taub, 1973). From certain studies, it is hypothesized that the reduced activity may mediate increased pain behavior found in animal models of chronic stress (da Silva Torres et al., 2003; Scheggi et al., 2002). A recent PET study in fibromyalgia patients by Wood and colleagues showed reduced presynaptic dopaminergic activity in several brain regions in which dopamine plays a critical role in modulating nociceptive processes (Wood et al., 2007), possibly highlighting dopaminergic dysregulation with functional pain disorders where stress is a prominent aggravating factor (Wood, 2004). Similarly to the endogenous opioid system, the issue of cause and effect between a "functional hypodopaminergic state" and pain has yet to be resolved. The observation that reduced pain thresholds in patients with Parkinson's disease normalized, with corresponding reductions in brain activation (insula and ACC), following administration of levodopa suggests that attenuation of dopaminergic activity underlies some chronic pain states (Brefel-Courbon et al., 2005). However, the current data from animal and patient studies on the role of dopamine mechanisms in pain, using either dopamine agonists or antagonists, are conflicting with regard to directionality (i.e., pro- or antinociceptive responses upon dopamine release) and location (i.e., nigrostriatal or mesolimbic pathways). A study by Scott and colleagues (2006) attempted to clarify this issue and showed that variations in the human pain stress experience are mediated by ventral and dorsal basal ganglia dopamine activity. Specifically, they found that activation of nigrostriatal dopamine D2 receptor-mediated neurotransmission was positively associated with individual variations in subjective ratings of sensory and affective qualities of pain; contrasting this, mesolimbic dopamine activation was only associated with variations in the emotional responses of the individual

during the pain challenge (i.e., increases in negative affect and fear ratings).

Such molecular imaging studies are providing highly novel information regarding pain processing in humans. Although the data are not conclusive regarding causality, it clearly shows that the brains of patients suffering chronic pain are fundamentally disturbed in ways neither considered nor appreciated before. New avenues for exploration and possible treatment targets are open, and this area is becoming an active area of exploration.

Novel Areas of Investigation

As the problem of pain and the key role of the brain becomes increasingly well recognized, more research is being directed toward a better understanding of the underlying mechanisms. Some of the newest and more novel areas of investigation are briefly summarized here.

Structural Imaging

The recent finding that significant atrophy exists in the brains of chronic pain patients (Apkarian et al., 2004b; Grachev et al., 2000; Schmidt-Wilcke et al., 2005) highlights the need to perform more advanced structural imaging measures and image analyses to quantify fully these effects. Determining what the possible causal factors are that produce such neurodegeneration is difficult. Candidates include the chronic pain condition itself (i.e., excitotoxic events due to barrage of nociceptive inputs), the pharmacological agents prescribed, or perhaps the physical lifestyle change subsequent to becoming a chronic pain patient. Carefully controlled longitudinal studies are now needed as this rapidly becomes, along with diffusion tractography studies to detect and quantify white matter tracts, an active area of research. Such studies might best be performed in animals.

Spinal Cord Imaging

Clearly, to determine the extent of changes present within the CNS, we must develop methods that allow noninvasive access to the changes within the human spinal cord. There is an extensive literature from animal studies regarding nociceptive processing within the dorsal horn to draw upon, and recent technical developments provide hope that translation to human studies will be soon feasible (Brooks et al., 2006; Maieron et al., 2007).

Imaging Microglial Activation

Recently, there has been considerable excitement over the possible role that microglia play in the development and maintenance of chronic pain states (Watkins et al., 2001). To translate these exciting animal findings to humans requires an ability to perform in vivo imaging of the recruitment of microglial and macrophages into the spinal cord and brain during the development of chronic pain states. Ultrasmall, superparamagnetic particles of iron oxide (or USPIO) are nanoparticles that might provide, like the PET ligand PK11195, an indication of microglial and macrophage recruitment (Bonnemain, 1998; Bulte and Frank, 2000; Banati, 2002). Linking these studies to those being currently performed provides an ideal opportunity to further explore the functional role of microglial in developing chronic pain states.

Genetics

We cannot ignore the possibility that our genes influence both how nociceptive stimuli are processed and how the brain reacts to peripheral injury and increased nociceptive inputs. Similarly, we cannot ignore the central role that our life experiences have on both these processes. Coghill and colleagues (2003) addressed the issue that some individuals claim to be "sensitive" to pain, whereas others claim they tolerate pain well. In their experiment, individuals who rated the pain highest exhibited more robust pain-induced activation of S1, ACC, and PFC compared with those who rated pain lowest. The key question is whether this increased pain report and correlated objective readout is nature or nurture driven. The answer is perhaps central to a better understanding of why certain patients develop chronic pain syndromes and others do not and perhaps explaining differences in treatment outcomes. Similarly, if these observations are driven by nurture, what influences in a person's upbringing are relevant for altering nociceptive pathways to again alter the processing and resultant pain perception? Studies are beginning to link genetic influences on human nociceptive processing with physical processes within the brain. Zubieta and colleagues (2003) examined the influence of a common functional genetic polymorphism affecting the metabolism of catecholamines on the modulation of responses to sustained pain in humans using psychophysical assessment and PET. Individuals homozygous for the met158 allele of the catechol-O-methyltransferase polymorphism (val158 met) showed diminished regional mu-opioid system responses to pain (measured using PET) and higher sensory and affective ratings of pain compared with heterozygotes. This provides clear evidence that our genes influence nociceptive processing within the brain and consequently our pain experience. The link between our genes and pain perception during acute and chronic pain experiences is one of the most exciting areas of pain research at present and is being led primarily by animal studies but with fast translation to human studies (Tegeder et al., 2006). Novel genes are being identified that force us to reconsider pain mechanisms as they relate to disease and perception. The hope is that this will lead to novel treatments that provide better efficacy for patients.

Conclusion

We have attempted to summarize from a largely systems neural-processing perspective the current state of knowledge regarding how pain is perceived during varying circumstances. We propose a central role for the brainstem and the descending pain modulatory system in affecting the resultant pain experienced. Anatomical-, functional-, molecular-, and tractography-based studies are further elucidating connectivities between subcortical and cortical structures to specific regions of the brainstem. This provides a framework for integrating nociceptive inputs with top-down influences so that appropriate

modulation of these inputs, prior to higher-order processing, is achieved to ensure the resultant pain experienced is appropriate for that particular circumstance. In the chronic pain state, we believe this integration is disrupted via both bottom-up and top-down influences, contributing to the generation and maintenance of a heightened pain experience.

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