Imaging pain

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Pain that persists or recurs for more than 3 months is defined as chronic and as such is one of the largest medical health problems in the developed world. Although the management and treatment of acute pain is reasonably good, the needs of chronic pain patients are largely unmet, creating an enormous emotional and financial burden to sufferers, carers, and society. Improvements in our ability to diagnose the causes of chronic pain are desperately needed. Furthermore, the pharmaceutical industry is struggling to find new and better drugs to treat chronic pain sufferers. Innovative methods that can aid decisions regarding choice and targeting of treatments alongside conventional clinical measures are therefore needed. Neuroimaging methods have the capacity to fulfil this need as they provide a non-invasive, systems-level understanding of the central mechanisms involved in pain processing. To date, the focus has been to dissect the physiological, psychological, and cognitive factors that influence nociceptive inputs to alter pain perception in healthy subjects and patients suffering from chronic pain. Obtaining reliable objective information related to the individual’s subjective pain experience provides a powerful means of understanding not only the central mechanisms contributing to the chronicity of pain states but also the potential diagnostic information. Identifying non-invasively where plasticity, sensitization and other amplification processes might occur along the pain neuraxis for an individual and relating this to their specific pain experience or measure of pain relief is therefore of considerable interest to the clinical pain community and pharmaceutical industry. In this review, I shall briefly summarize our current state of knowledge regarding the central representation of pain perception in varying situations.

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Imaging the brain: methods available

Figure 1 illustrates the main imaging modalities in use today and what physiological correlate of brain activity they measure. The time delay between neural activity and the increased haemodynamic response that blood oxygen level dependent (BOLD)-functional magnetic resonance imaging (FMRI) detects is between 6 and 9 s; this means that BOLD-FMRI-related brain activity cannot provide temporal information regarding which brain region activated first, second, and so on. This ‘cost’ or balance between the spatial and temporal information achievable, and how ‘invasive’ you have to be if you want ‘it all’, is illustrated in Figure 2. Both these graphs, therefore, usefully demonstrate that when choosing your imaging modality there are pros and cons that must be considered dependent upon your hypothesis and goal. Other methods provide different sorts of information about the brain (i.e. structural or metabolic) and at the end of this review I shall provide a few examples of where these newer ways of examining the human brain are providing exciting and highly novel information regarding the condition of a chronic pain patient’s brain.

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 therefore not always 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, a condition that affects ~20% of the adult population. Furthermore, the behavioural 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 of The International Association for the Study of Pain: ‘An unpleasant sensory and emotional experience associated with actual or 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 3 illustrates the mixture of physical, cognitive, and emotional factors that we now know influence nociceptive inputs to either amplify or attenuate pain intensity, yet also provide the richness or ‘colour’ to the experience. We know also from the recent data that a painful or unpleasant experience can result without a nociceptive input, 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 dissect their contribution has only been feasible since neuroimaging tools allowed us non-invasive access to the human CNS. Determining the balance between peripheral vs central influences, and ascertaining which are a result of pathological vs emotional or cognitive influences will clearly aid decisions regarding the targeting of treatments (i.e. whether to use pharmacological, surgical, cognitive behavioural, or physical rehabilitation as your preferred option). This is perhaps where imaging might provide its greatest contribution in the field of pain.

The ‘cerebral signature’ for pain

Because pain is a complex, multifactorial subjective experience, a large distributed brain network is accessed during nociceptive processing; this is often called the ‘pain matrix’ and simplistically can be thought of as having lateral (sensory–discriminatory involving areas such as primary somatosensory (S1), secondary somatosensory (S2), thalamus, and posterior parts of insula) and medial [affective–cognitive–evaluative involving areas like the anterior parts of insula, anterior cingulate cortex (ACC), and prefrontal cortex (PFC)] neuroanatomical components. 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), the pain matrix is not a defined entity. A recent meta-analysis of human data from different imaging studies provides at least some clarity regarding the commonest regions found active during an acute pain experience as measured by positron emission tomography (PET) and FMRI (and see Fig. 4). These areas include: S1 and S2, insular, ACC, PFC, and the thalamus. This is not to say these areas are the fundamental core network of human nociceptive processing (and if ablated would cure all pain), although studies investigating pharmacologically induced analgesia do show predominant effects in this core network, suggesting perhaps their importance in influencing pain perception. 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 (see Fig. 3). A cerebral signature for pain is perhaps a more useful term, especially when considering the neural representation of chronic, ongoing, or spontaneous pain in patients that appears not to be represented necessarily by the conventional ‘pain matrix’ concept.

To understand how nociceptive inputs are processed and altered to subsequently influence changes in the pain
experienced, it is useful to examine separately the main factors listed in Figure 3 that alter pain perception.

Genetics

The possibility that our genes influence both how nociceptive stimuli are processed and how the brain reacts to peripheral injury and increased nociceptive inputs cannot be ignored. Similarly, the central role that our life experiences have on both of these processes cannot be ignored. Coghill and colleagues\(^{11}\) addressed the issue that some individuals claim to be ‘sensitive’ to pain, whereas others claim they tolerate pain well. In the trial, individuals who rated the pain highest exhibited more robust pain-induced activation of S1, ACC, and PFC compared with those who rated pain the lowest. The key question is whether this increased pain report and correlated objective readout is nature or nurture driven. Studies are beginning to link genetic influences on human nociceptive processing with physical processes within the brain. Zubieta and colleagues\(^{81}\) 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 (val158met) showed diminished regional mu-opioid system responses to pain (measured using PET) and higher sensory and affective ratings of pain compared with heterozygotes. This is one of the more exciting areas of neuroimaging research at present; however, more studies are needed to validate and extend these findings.

Cognition: attention and distraction

We know from experience that attention is very effective in modulating the sensory and affective aspects of pain. FMRI and neurophysiological studies showed attention- and distraction-related modulations of pain-evoked activations in many parts of the pain 'matrix'. From these studies, regions that appear critical during the attentional modulation of pain include the descending pain modulatory system and key elements of the pain 'matrix'.

The descending pain modulatory system

This is a well-characterized anatomical network that enables regulation of nociceptive processing (largely within the dorsal horn) in various circumstances to produce either facilitation (pro-nociception) or inhibition (anti-nociception). The pain-inhibiting circuitry, of which the periaqueductal grey (PAG) is a part, is best known and contributes to environmental (e.g. during the fight or flight response) and opiate analgesia. 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 below).

In an early study using high-resolution imaging of the human brainstem, we showed significantly increased activity within the periaqueductal grey 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. Valet and colleagues extended the work further and showed that the cingulo-frontal cortex exerts top-down influences on the PAG and posterior thalamus to gate pain modulation during distraction. These studies, and others, provide clear evidence for the involvement of brainstem structures in the attentional modulation of pain perception, and recent work using diffusion tractography confirms that white matter anatomical connections exist between cortical and brainstem regions in the human brain, thereby enabling such top-down influences.

Context: the placebo effect

Work in humans has helped provide a framework by which the placebo effect and subsequent analgesia is mediated. Again the brainstem is critically involved in mediating placebo analgesia. Descending influences from the diencephalon, hypothalamus, amygdala, anterior cingulate cortex (ACC), insular and prefrontal cortex (PFC) that elicit inhibition or facilitation of nociceptive transmission via brainstem structures are thought to occur during placebo analgesia. Using PET, Petrovic and colleagues confirmed that both opioid and placebo analgesia are associated with increased activity in the rostral ACC, but they also observed a co-variation between the activity in the rostral ACC and the brainstem during both opioid and placebo analgesia, but not during pain alone. Wager and colleagues extended these observations to consider whether or not placebo treatments produce analgesia by altering expectations. Using a conditioning design, the authors 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 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. This is consistent with the concept that prefrontal mechanisms can trigger opioid release within the brainstem and, thereby, influence the descending pain modulatory system to modulate pain perception during the placebo effect.

Mood

For both chronic and acute pain, the sufferer’s mood and emotional state has a significant impact on 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 but for the chronic pain patient it becomes maladaptive and can lead to fear of movement, avoidance, anxiety, and so forth. Studies aimed at understanding how anticipation and anxiety cause a heightened pain experience have been performed using imaging methods and novel paradigm designs. Critical regions involved in amplifying or exacerbating the pain experience include the entorhinal complex, amygdalae, anterior insula, and prefrontal cortices. Some of these brain regions are not commonly found active in pain studies (notably, the
entorhinal complex and therefore if found active, strongly indicate anxiety as a critical factor in a subject's pain experience. More recent studies confirm the role of these brain regions in amplifying pain in patients suffering somatoform pain disorder and rheumatoid arthritis, and also identifying how activity within this region produces increased pain intensity.

With regard to mood, depressive disorders often accompany persistent pain. 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 that may mediate their interaction. An FMRI study showed that activation in the amygdala and anterior insula differentiated patients with fibromyalgia with and without major depression. Another study on fibromyalgia patients found that pain catastrophizing (defined as a set of negative emotional and cognitive processes), 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, DLPFC), emotional aspects of pain (claustrum, closely connected to amygdala), and motor control. The construct of catastrophizing incorporates magnification of pain-related symptoms, rumination about pain, feelings of helplessness, and pessimism about pain-related outcomes. The results by Gracely and colleagues support the notion that catastrophizing influences pain perception through altering attention and anticipation, and also heightening the emotional responses to pain. In our study on rheumatoid arthritis patients, we found that despite an overall lower disease activity in patients with significantly higher depression scores, they complained of more painful joints. The interaction between their depression and brain activity in response to a joint squeeze was mediated via the medial PFC that, in turn, communicates to limbic brain regions including the entorhinal complex. This study illustrates the utility of imaging in possibly highlighting where the pain 'problem' is for those patients with more depression and therefore perhaps aiding selection and targeting of treatment options.

**The PFC: controlling pain**

It is clear from these few studies described and others in the literature that pronounced PFC activation is consistently found across clinical pain conditions, irrespective of underlying pathology. We are beginning to unravel only now the roles of specific PFC regions in pain perception; it is thought that they reflect emotional, cognitive, and interoceptive components of pain conditions, and also perhaps processing of negative emotions, response conflict, and detection of unfavourable outcomes in relation to self for more medial PFC. Baliki recently showed in chronic back pain patients increased medial PFC, including rostral ACC activity during episodes of sustained high ongoing pain. Furthermore, the medial PFC activity was strongly related to the intensity of chronic back pain. In other studies, connectivity analyses of functional imaging data have also highlighted the relevance of frontal cortical regions in mediating or controlling the functional interactions among key nociceptive-processing brain regions that subsequently produce changes in perceptual correlates of pain, independent of changes in nociceptive inputs. A specific role for the lateral PFC as a 'pain control centre' has been advanced in a study of experimentally induced allodynia in healthy subjects. 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 examining other issues related to the control of pain and personal level of 'control belief' or how high an internal locus of control you have, and also higher order reappraisal mechanisms, firmly place the PFC as a site of major significance. Future studies are focusing on this complex region.

It is important to also note that the PFC (specifically the DLPFC) is a site of major neurodegeneration and potential cell death in chronic pain patients. These latest findings suggest that severe chronic pain could be considered a neurodegenerative disorder that especially affects this region. However, determining the possible causal factors that produce such neurodegeneration is difficult. Candidates include the chronic pain condition itself, the pharmacological agents prescribed or perhaps the physical lifestyle change subsequent to becoming a chronic pain patient. Carefully controlled longitudinal studies are needed.

**Psychogenic pain or pain without a nociceptive input**

Recent imaging data display activity of the near entire 'pain matrix' without any nociceptive input, suggesting it is time to reconsider how central pain processing is defined with respect to the origin of the input and resultant perception and meaning. This is not to say that 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 as a result of the extensive neural activation that occurs. Rather, these studies illustrate how powerful the mind can be in terms of activating specific networks within the brain to subsequently produce a realistic and vivid experience.

**Injury**

Recently, changes within the descending pain modulatory network have been implicated in chronic pain (central sensitization) and in functional pain disorders. 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 regarding the differential involvement of the periaqueductal grey (PAG), rostroventromedial medulla (RVM), parabrachial nucleus (PB), dorsal reticular nucleus, and nucleus cuneiformis (NCF) in the generation and maintenance of central sensitization states and hyperalgesia in both animal models and, for the first time, in a human model of secondary hyperalgesia.90 Recent clinical studies are further highlighting how dysfunction within the descending modulatory system can be sufficient to generate key symptoms of chronic pain. A study by Wilder-Smith and colleagues75 investigated whether patients with irritable bowel syndrome had hypersensitivity and pain upon distension as a result of abnormalities in endogenous pain inhibitory mechanisms; they found this to be the case for patients compared with controls. Mayer and colleagues40 recently examined whether visceral hypersensitivity found in patients with IBS might arise as a consequence of a top-down descending influence. 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 suggests that the 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.

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 in other studies.96 98 Furthermore, recent pharmacological studies are highlighting the influence of gold-standard agents used to treat key symptoms of neuropathic pain (i.e. gabapentin) on such brainstem structures.29

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 in developing mechanism-based therapies for treating different types of acute and chronic pain.

Spinal cord imaging: the next frontier

Clearly, to determine the extent of changes present within the entire CNS, we must also develop methods that allow non-invasive access to changes within the human spinal cord. This is a challenging region to image because of the low signal to noise as a result of its small size and the considerable motion-related artifacts because of respiration, the cardiac cycle, and pulsation of cerebrospinal fluid. However, technological developments are opening up this part of the pain neuraxis for examination, and further study and early results look promising.9 39

Altered opiodergic and dopaminergic pathways: the brain substrate is sick

The availability of PET ligands for opioid and dopamine receptors has allowed the study of these receptor systems in several clinical pain states. Early opioid ligand studies30 showed decreased binding in patients with chronic pain that normalized after reduction of their pain symptoms. Regional differences in ligand binding have recently been found in neuropathic pain studies31 32 76 with decreased binding in several key areas involved in pain perception. The dopaminergic pathways have also been implicated in pain processing in animal2 and patient studies.26 A recent PET study by Wood and colleagues79 showed reduced presynaptic dopaminergic activity in fibromyalgia in several brain regions in which dopamine plays a critical role in modulating nociceptive processes. Interestingly, another study by Scott and colleagues61 showed that variations in the human pain stress experience are mediated by ventral and dorsal basal ganglia dopaminergic activity. Similar to the endogenous opioid system, the issue of cause and effect between a ‘functional hypodopaminergic state’ and pain has yet to be resolved.

However, what is clear is that the brains of chronic pain patients whose analgesic needs are largely unmet with current treatment options are very sick, both in terms of neurotransmitter systems and potential extensive neurodegeneration, as now shown in several studies across varying pain conditions.27 34

Conclusion

Knowledge regarding how pain is perceived at a central level in humans is growing. An extensive network is recruited that is highly modifiable depending upon genetics, the environment, mood, and the particular injury sustained. Combined, these produce a unique cerebral signature that produces an individualized pain experience.

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