Pain mechanisms and their disorders

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The purpose of this article is to summarise how functional imaging techniques have changed our understanding of normal and abnormal pain mechanisms, how they inform a change in clinical practice and to speculate on possible future clinical uses.

The experience of pain can only be defined in terms of human consciousness. Functional imaging techniques have made it possible to identify the main cerebral components of the human nociceptive system. These comprise at least two main human nociceptive systems working in parallel called the medial and lateral pain systems (Fig. 1). This has provided a physical construct for the concept of the human pain matrix. We are just beginning to understand the division of function within these systems, providing the possibility of establishing a more rational framework for pain therapy.

There is a spectrum of pain experience from pain that may closely reflect physical events in tissue (e.g. leading to excitation of nociceptors – nociceptive pain), to pain that is generated without any peripheral physical input (e.g. psychogenic and neuropathic pain). The brain is, therefore, acting as a virtual reality system that may or may not be constrained by interactions with the body’s internal and external environment. In order to understand these interactions, non-invasive methods for measuring cerebral responses in man are required. Functional imaging techniques provide the means to understand some of the molecular events underpinning these interactions, which have been recently reviewed.

The purpose of this article is to summarise how functional imaging techniques have changed our understanding of normal and abnormal pain mechanisms, how they inform a change in clinical practice and to speculate on possible future clinical uses. No new major classes of analgesic have been developed in the last century apart from the extended role of tricyclic antidepressants as adjunct analgesics and 5-HT1a agonists for migraine. There are many reasons for this, but one may have been the difficulty in translating animal models of pain to adequate proof-of-concept trials in humans.
The other problem relates to the assumption that modulation of nociceptive processing at any level may alter pain experience. This particularly applies to pharmacological agents, which may have very different effects at different sites within the nervous system. A classic example is capsaicin, which is strongly algesic at the periphery and dorsal horn of the spinal cord, but analgesic when injected intracerebroventricularly. Functional imaging provides the means to measure integrated nociceptive processing in the brain, to define pathophysiological mechanisms of some of the main clinical pain states and to define potential therapeutic targets. Some of these techniques have already provided well-defined targets for new classes of analgesics.

Although there is no established role for functional imaging in pain management, there may be a greater role for functional imaging in patient assessment, analgesic development and response monitoring.

Scope and limitations of functional imaging for the study of pain

Electrophysiological techniques (pain-evoked potentials, EEG frequency analysis and MEG), PET and fMRI provide access to nociceptive processing mainly within the brain. However, recent studies have extended some of these approaches to the spinal cord. Only [18F]-fluorodeoxyglucose ([18F]-FDG) PET and electrophysiological techniques provide direct measurement of neuronal activity and, therefore, currently provide the most robust measure of drug modulation of nociceptive activity. Electrophysiological techniques with their millisecond temporal resolution provide the means to study early attentional and anticipatory components of nociceptive processing. Improved techniques for source localisation of pain-evoked potentials have provided greatly improved spatial resolution with millimetre reproducibility. Improved techniques for MEG analysis (SAM analysis) provide a ‘spm’-like approach to complex data sets. PET has provided the means to measure both metabolic and neurochemical aspects of nociceptive processing. This has allowed the identification of receptor systems and changes in their occupation during acute and chronic pain, in addition to imaging aspects of cholinergic and dopaminergic transmission. The great advantage of fMRI over PET is that it is possible to make repeated measures of nociceptive responses without the constraints imposed by the use of radioactivity, allowing much more complex experimental design.

The weakness of all these techniques is that in the final analysis we are left with significant blobs on brain volumes without directional information and without information about the ascending or descending nociceptive inputs from which they result. They can, therefore, only be
interpreted with reference to detailed anatomical and pharmacological studies derived from animal\textsuperscript{13–16} and human \textit{post mortem}\textsuperscript{17} studies. This, together with information from evoked potentials and MEG, can begin to provide a working model of the circuitry concerned with nociceptive processing.

This approach has provided some significant insights into human pain perception that would not have been possible from extrapolation from studies in animals in isolation. The combined use of different techniques such as opiate receptor imaging with functional studies has already provided some important insights into the integration of different neurochemically defined systems within the brain\textsuperscript{18}. Electrophysiological techniques have provided some information on the temporal sequence of nociceptive processing within the pain matrix, and improved techniques will provide the greater detail required for a dynamic model of nociceptive processing\textsuperscript{19}.

The most important feature of functional brain imaging techniques is that they are able to measure many aspects of nociceptive processing, such as anticipation of pain and neurochemical changes associated with pain, which cannot be measured by any other means.

\textbf{Acute and chronic nociceptive processing in the human pain matrix}

There is a general consensus on the main components of the human pain matrix (Fig. 1)\textsuperscript{20}. It has been assumed for many years that the medial and lateral systems might respectively be concerned with processing chronic and acute pain\textsuperscript{21}. Functional imaging studies have provided unequivocal evidence that this is not the case. Both systems are involved in acute nociceptive processing and at least one type (neuropathic) of chronic pain and these are processed in parallel\textsuperscript{4}.

It has been traditional to think of acute and chronic pain as being very distinct processes possibly with certain types of chronic pain being processed within discreet brain regions. At a clinical level, many types of chronic pain such as arthritic pain are a mixture of recurrent acute pain and chronic on-going pain. It is difficult to see an empirical advantage of processing each type of pain in a separate and discrete nociceptive system. So far, there is very little evidence from imaging studies for a division of function within the pain matrix on the basis of the temporal components of pain\textsuperscript{4,22}.

However, there may be some more subtle differences between acute and chronic pain processing. Components of the lateral system such as the primary somatosensory (SI) cortex do appear to be as frequently activated with tonic (non-phasic experimental pain) and phasic pain (67\% and 69\% of studies show activations, respectively). But only 23\%
of studies of chronic on-going clinical pain demonstrated activation of SI. There are a number of potential reasons for this. Nociceptive projections to SI are sparse. Also, this is the only area where functional imaging experiments have demonstrated any convincing somatotopy for pain. Therefore, summation of responses to chronic pain in different locations may dilute the signal change in SI. Responses within the medial system appear to be predominantly bilateral and non-somatotopic. Acute pain experiments tend to stimulate the same or adjacent locations, whereas chronic pain experiments often include patients with variable...
pain locations and, therefore, may spatially dilute an already weak signal in SI. However, it may be that signals in SI and other components of the lateral system are faster and more short-lived.

A further reasons to distinguish between acute and chronic pain are the clear time-dependent neurochemical changes that occur, for instance in the spinal cord, in various sub-acute pain models. This has lead to the general belief that there must be important pharmacotherapeutic differences between acute and chronic pain. However, so far, there is no evidence for any class of analgesic only being effective in the acute or chronic phase of any type of pain. Such differences may exist, but they have yet to be clearly demonstrated in man.

What factors affect the pattern of nociceptive processing in the brain?

In terms of responses to experimental pain, it is now very clear that the psychological context of the stimulus in terms of anticipation and attention are as important as the stimulus parameters. It had been previously thought that anticipation might only activate certain components of the medial system such as medial prefrontal cortex and anterior cingulate cortex, and that these areas were adjacent and discrete from those activated by pain. Subsequent studies however, suggested that these responses could be blocked by benzodiazepines and therefore, may be more related to anxiety than anticipation of pain per se. More recently, it has been shown that most of the nociceptive system can be activated by anticipation of a painful stimulus, the anticipatory responses are just smaller than the pain intensity-related responses. Further evidence for the importance of top-down effects comes from a number of studies showing the effects of altered attention on nociceptive processing. Altered cingulate responses during different attentional instruction have been interpreted in the context of differences is coping strategies.

These studies provide clear evidence for top-down influences on nociceptive processing. They also help the interpretation of earlier clinical studies where substantial differences in responses to thermal pain stimuli were observed in patients with different types of clinical pain. Responses to standardised acute thermal pain stimuli were reduced in patients with acute (post-dental extraction) inflammatory pain and on-going chronic (arthritic) pain compared to controls. Patients with chronic psychogenically-maintained pain (atypical facial pain) demonstrated enhanced response to acute thermal stimulation compared to controls in the anterior cingulate cortex. The enhanced responses were thought to represent abnormal attention to the affective processing.
of nociceptive inputs that might contribute to the perseverance of chronic pain in these individuals. The observation that attention can profoundly affect the pattern of nociceptive responses within the pain matrix gives some credence to this concept. However, more recent studies in patients with low back pain and depression did not demonstrate significant differences in nociceptive processing between this group and pain-free controls.

**Endogenous modulation systems and division of function within the pain matrix**

There are still relatively few studies of endogenous pharmacological modulation of human nociception. PET studies have demonstrated changes in opioid receptor binding in chronic neuropathic and inflammatory arthritic pain in addition to acute experimental pain. These are consistent with increased occupation of opioid receptors during pain. These changes were predominantly within the medial system.

There is increasing evidence that the main division of function within the pain matrix is that the lateral system is more concerned with the sensory discriminative components, such as localisation and texture, whereas the medial system is more concerned with the affective and motivational components of nociception.

This is consistent with the neurosurgical observations that deafferentation of the anterior cingulate cortex in patients with chronic intractable pain produces a state where they still experience pain, but it no longer bothers them. This result is quite similar to the clinical observations of the effects of synthetic opiates which are rarely pain-ablative, but substantially reduce the unpleasantness of acute and chronic pain. Interestingly, the highest concentrations of opioid receptors are found in components of the medial pain system, such as the perigenual (underneath the anterior protrusion of the corpus callosum) cingulate cortex and medial thalamus. Whereas some of the cortical projections of the primary somatosensory cortex can be identified by their low opioid receptor binding. Preliminary observations in chronic pain suggest that synthetic opiates appear mainly to alter function within the projections of the medial system. Most of the changes that occur in opioid receptor binding in both acute and chronic pain are within the medial system. Recent observations suggest that placebo analgesia is, at least partially, mediated by endogenous opioid peptides and that opiate- and placebo-mediated analgesia share common circuitry in the anterior cingulate cortex.

There is, therefore, increasing evidence for the role of the medial pain system, in particular the anterior cingulate cortex, in the control of attention to the affective and motivational components of acute and
chronic pain. Synthetic and endogenous opiates probably both modulate cingulate nociceptive activity. Their cerebral mechanisms of action are still uncertain, but anatomical studies suggest mu opioid modulation of thalamocortical loops projecting through anterior cingulate cortex. The modulation of the breakdown of endogenous opioid peptides has been identified as a potential therapeutic target by a number of pharmaceutical companies.

Patterns of neural activity in different types of clinical pain syndrome

Pharmacological mechanisms have been demonstrated in the dorsal horn in association with neuropathic and inflammatory pain models that may contribute to some forms of allodynia (pain induced by sensory modalities such as touch that would not normally induce pain). However, in terms of what signals the brain sees, these spinal mechanisms convert what would normally be signalled in non-nociceptive ascending pathways to signals within the ascending nociceptive channels (ascending spinothalamic tracts). So far, there is no evidence in humans that such pains are processed within different brain structures when induced experimentally acutely (capsaicin induced allodynia) or when studied in patients with chronic neuropathic pain. However, there is a trend of reduced activity within the thalamus during the ongoing neuropathic pain. Formal comparisons with other types of pain have not been made, but it is possible that this may represent reduced activity of inhibitory inter-neurones within the thalamus.

Recently, the responses to allodynia to pressure in patients with chronic wide-spread pain (fibromyalgia) has been compared to responses to similar levels of pressure induced pain in pain-free volunteers and found to produce the same pattern of activity within the major components of the pain matrix.

In general, for most types of pain, there do not appear to be specific brain areas dedicated to specific types of pain. However, interesting preliminary studies in headache may provide a possible exception to this generalisation in that there seem to be more prominent subcortical activations than cortical activations. PET studies during headache have measured increased activity in the midbrain and pons in migraine and the hypothalamus during cluster headache. These observations ‘taken together with what is known about the mechanisms of these types of headaches may provide evidence for a neurovascular aetiology rather than a primary vascular mechanism’. However, it should be mentioned that all these areas are activated in other types of pain; therefore, if there is a specific pattern to these responses, it is likely to be related to the predominance of a subcortical pattern of activity rather than the specific structures involved.
It is too early to say whether it is possible to distinguish between different categories (nociceptive, neuropathic or psychogenic or even imagined) of pain using functional imaging. However, different patterns of response within the pain matrix are measurable in different pain syndromes and in different psychological contexts. More sophisticated methods for measuring different aspects of simultaneous processing within the pain matrix are emerging. It is possible that some of these may be used to categorise clinical pain syndromes, match them to appropriate treatments, and monitor response to such treatments in the future. This may particularly apply as the development and therapeutic costs of new treatments escalate.

**Drug development**

Functional imaging techniques have provided the means to identify components of the pain matrix and their specific functions. Careful study of these areas of the human brain has the potential to yield new classes of analgesic compounds. The use of functional imaging at a proof-of-concept stage of drug development has the potential for greatly reducing the costs of clinical development. PET provides the means to measure tissue concentrations of labelled drugs in brain and other tissues and also to measure changes in receptor occupancy. It is encouraging that there is now substantial investment in this area of research by the pharmaceutical industry.

**Physiological basis for the sub-classification of pain**

The International Association for the Study of Pain (IASP) has provided a classification of pain that includes 32 main groups of pain each with sub-classifications. Much of the classification relates to the place and system that the pain occurs in and its temporal characteristics. This has provided an invaluable basis for epidemiological studies and health-care planning. However, in terms of nociceptive processing, the temporal and spatial features of pain may be of less importance. This particularly applies to localisation, as most nociceptive processing within the medial system is non-somatotopic. There are no identifiable systems dedicated to processing pain of a particular type, location or duration and yet these assumptions provide a common framework for the organisation of pain services, pain trials and the teaching of medical students.

It may be more helpful to consider why certain types of pain such as neuropathic and psychogenically-maintained pains (somatoform pain disorders) are more likely to become chronic, than trying to make...
distinctions between acute and chronic pain that so far have no biological basis in man. The current practice of doing separate trials in acute and chronic pain may also be questioned on the same basis.

Conclusions

The brain does not share the construct for pain perception and treatment that the medical profession would like to impose on it. It is premature to reclassify pain on a physiological basis. When this does occur, it is likely to be simpler with less emphasis on localisation and duration, with greater emphasis on the psychological context of the pain and the pathophysiological mechanisms resulting in its maintenance.

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