

Brain imaging of clinical pain states: a critical review and strategies for future studies

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Research into brain imaging of pain is largely dominated by experimental acute-pain studies. Applied study paradigms have evolved a lot over past years and the ensuing results have furthered enormously our understanding of acute-pain processing. In sharp contrast, published work on brain-imaging in chronic pain remains scant. Furthermore, the results of these studies are highly incongruent, which could be explained by the fact that patient populations studied varied largely in terms of pain history, pain distribution, cause of pain, and psychological set-up. To circumvent these problems, several investigators have used surrogate models of neuropathic pain, but the validity of these models is highly questionable. In this Review we critically discuss the problems and shortcomings of most published reports on chronic pain and we propose some strategies for future studies. We argue that the post-operative pain model is highly appealing since it opens perspectives for prospective longitudinal studies with repeated assessments and it enables control for many confounding factors, which hamper the interpretation of most current studies. We also plead for a multimodal imaging approach in which classic brain-activation studies are supplemented with genetic, neurochemistry, brain morphometry, and transcranial magnetic stimulation studies.

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Introduction

Modern brain-imaging studies such as PET, functional MRI, and, more recently, magnetoencephalography (MEG) have opened exciting new avenues for non-invasive exploration of brain mechanisms implicated in acute and chronic-pain processing. The physiological signals measured by these three techniques are different and the question of which technique to use is co-determined by the particular neurophysiological question that is being addressed (panel 1, figure 1, table). Most pain-imaging studies have investigated forms of acute nociceptive pain. Few brain-imaging studies have been devoted to the mechanisms associated with chronic pain and the results of these studies are often inconclusive with some arguing that there are no differences in the processing of acute and chronic pain and others concluding the opposite. This discrepancy might be explained, at least in part, by the fact that most studies investigating non-experimental forms of pain are based on relatively small samples of patients, include patients with different pain pathologies, or lack appropriate controls.

The aim of this Review is to critically discuss brain-imaging studies of clinical pain. We will not cover the published work on visceral pain and chronic forms of pain with unknown pathophysiology, such as chronic low-back pain, fibromyalgia, irritable bowel syndrome, etc. We will also discuss important methodological issues that have not been or have insufficiently been addressed by the brain-imaging community and will propose strategies for future brain-imaging studies, focusing on longitudinal studies investigating the transition from acute to chronic pain.

Imaging of acute, experimental pain

The pain system is divided into a lateral and a medial system.¹ The lateral pain system consists of spinothalamic

Panel 1: Brain imaging techniques

PET

- Requires relatively long pain stimulation periods (40–60 s).
- Different functional states (eg, pain and rest) are always acquired in separate scans.
- Maximum number of scans that can be acquired is limited by radioactivity dose restraints.
- Usually requires multi-patient study designs.
- Potential to map neurotransmitter systems and drug uptake in vivo and molecular imaging.
- Provides a solution in cases where fMRI cannot be accomplished because of contraindications.

fMRI

- Offers better temporal and spatial resolution than PET.
- Pain stimuli do not need to be applied over a long period.
- The control state and the active pain condition are done in the same run.
- Better suited than PET for studying cognitive effects on pain processing.
- Unlimited amount of repetitions within a single patient, allowing single participant and follow-up studies.
- Offers less comfort to the patient (noise, body constrained in the magnet bore).
- Requires expensive fMRI-compatible stimulation and monitoring equipment.

MEG

- Allows mapping of the sequential activation of brain structures in pain processing.
- Provides a direct measure of neuronal activity.
- The most ecological technique with the highest comfort and least distress for participants.
- Allows conclusions from single trial and single participant studies (great clinical potential).

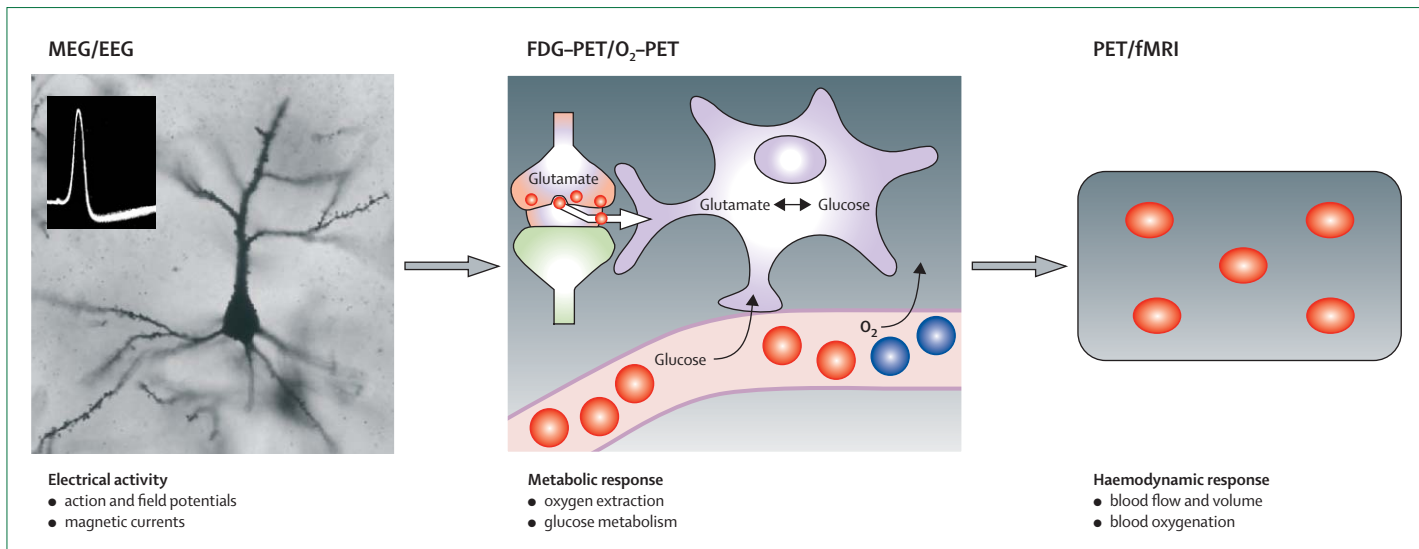


Figure 1: Brain imaging techniques used in the study of pain
MEG and EEG provide the most direct measures of neuronal activity, whereas the two most commonly used techniques (PET and fMRI) measure an indirect haemodynamic response.

tract neurons projecting from the ventrobasal nucleus of the thalamus to the primary and secondary somatosensory cortex, parietal operculum, and the insula. By contrast, the medial pain system includes the spinothalamic tract neurons projecting to the intralaminar and medial thalamic nuclei and further to the anterior cingulate cortex, the amygdala, the hippocampus, and the hypothalamus, the spinoreticular projections to the parabrachial nucleus and the locus coeruleus, and the spinomesencephalic tract projections to the periaqueductal grey matter. Whereas the lateral pain system is mainly associated with the sensory-discriminative aspects of pain processing, the medial pain system plays a crucial part in the motivational-affective and cognitive-evaluative aspects of pain processing, memory for pain, and the autonomic-neuroendocrine responses. By use of various experimental paradigms, imaging techniques, and types of experimental pain (mechanical, thermal, chemical, tonic *vs* phasic), brain-imaging studies have described with a relatively high consistency a set of brain areas that

are activated by a painful stimulus. Among these, the most commonly activated areas are the insula, anterior cingulate cortex, primary and secondary somatosensory cortices, primary motor and premotor cortices, supplementary motor area, thalamus, prefrontal and posterior parietal cortices, basal ganglia, midbrain (periaqueductal grey matter), and cerebellum. Together, this set of brain areas is often referred to as the pain matrix. The so-called pain matrix includes areas such as primary motor cortex, supplementary motor area, cerebellum, and prefrontal cortex, which do not belong to either the lateral or medial pain system. The concept of the pain matrix is controversial and there is no real consensus as to which areas exactly make part of it. Moreover, to which extent individual parts of the matrix are required for forming the conscious experience of pain is unclear. Finally, parts of the pain matrix are also activated by various non-painful stimuli or conditions such as warmth, itch, negative emotions, stress, blood-pressure changes, thirst, hunger, and air hunger. A detailed discussion of the respective roles of these areas in acute-pain processing falls outside the scope of this Review, but has been reported elsewhere.^{2,3}

There is ample evidence that the brain-activation pattern produced by a noxious stimulus is to a large extent co-determined by top-down processes.⁴ The psychological variables that have been most thoroughly studied are attention and distraction, expectation, and anxiety. Other examples of such top-down effects can be found in some recent brain-imaging studies on the placebo effect.⁵⁻⁷

Imaging of clinical pain

Compared with the vast published research on brain imaging related to the processing of acute experimental

	Temporal resolution	Spatial resolution	Advantages	Disadvantages
PET	>40 s	>4 mm	Measures activity in cortical and subcortical structures. Stimulus-independent technique. Allows receptor binding studies	Radioactivity. Poor temporal resolution. Invasive technique. Limited amount of scans possible.
fMRI	100 ms–3 s	>2 mm	Measures activity in cortical and subcortical structures. Excellent spatial resolution.	Poor patient comfort. Requires non-magnetic equipment. Stimulus-dependent technique.
MEG	milliseconds	>2 mm	Excellent temporal resolution. High patient comfort. Ecological method.	Difficulties to measure subcortical activity. Requires non-magnetic equipment. Stimulus-dependent technique.

Table: Characteristics of different brain imaging techniques used in the study of pain

pain and the psychological processes associated with its top-down modulation, the research on clinical pain processing is rather sparse. Additionally, methodological difficulties make the results of most studies difficult to interpret or to generalise to a larger population. Three approaches have been followed in the study of brain processes underlying chronic pain. In the first approach, sensory disturbances characteristic of clinical pain—eg, thermal and mechanical allodynia or hyperalgesia—are experimentally induced in normal volunteers. The best-known example is the capsaicin model, which has been used as a model for neuropathic pain.^{8,9} The second approach has been to scan patients with clinical forms of pain and to compare brain activation patterns measured after stimulation of a painful and a non-painful body area.^{10–15} Alternatively, changes in brain-activation patterns are compared in patients in their habitual pain state and after an analgesic intervention.^{16–20} Finally, brain responses to painful stimulation in pain patients have been compared with those in healthy individuals submitted to the same stimuli.^{21–23}

Brain activation studies

The first studies focused on baseline brain metabolism in a chronic pain state and compared either the pain condition with a pain-free condition after a therapeutic intervention or brain activity across hemispheres.^{16,17,24,25} They reported either a reduction in thalamic activity in cancer patients with pain due to brachial or lumbar plexus invasion of the tumour¹⁶ and in patients with mononeuropathic pain in the lower extremities after nerve injury¹⁷ or thalamic hyperactivity contralateral to the painful side in patients with central post-stroke pain.²⁴ The purported role of the thalamus in neuropathic pain was further underscored by results from MEG studies showing the presence of a distinct increase in low-frequency activity in the τ range.^{26,27} These studies are hard to interpret because they used small and heterogeneous samples of patients and lack a control for non-specific effects of the therapeutic intervention. Finding homogeneous populations of patients has proven difficult for most reports, with the exception of studies in migraine and cluster headache, possibly explaining why the data in these conditions are the most converging and conclusive of the published research of chronic pain.

Cluster headache and migraine

Cluster headache and migraine are episodic pain syndromes that pose particular challenges for brain-imaging studies. Several investigators have preferred to experimentally evoke a cluster headache or migraine attack rather than to wait for a spontaneous attack to occur. This situation is different from the clinical situation where the onset of the attack cannot be predicted, and thus pain coping mechanisms may be triggered that could significantly affect brain-activation patterns.²⁸

Weiller and colleagues²⁹ showed that migraine headache is associated with a significant increase in regional cerebral blood flow (rCBF) in dorsal and median brain-stem structures. This activation persisted after the headache had been successfully treated with sumatriptan. This finding was confirmed in more recent brain-imaging studies in spontaneous and evoked migraine.^{30–33} These studies further showed that the dorsal pontine activation is lateralised to the side of the migraine attack. Most studies also reported a strong activation in prefrontal cortex and cerebellum but not in other parts of the pain matrix.

In sharp contrast, both nitroglycerin-induced and spontaneous cluster headache are associated with a prominent activation in the ipsilateral inferior hypothalamus.^{34–37} Additional increases in rCBF were observed in the insula, right anterior cingulate cortex, right inferior frontal cortex, contralateral thalamus, and cerebellum, but not in the primary or secondary somatosensory cortices or brain stem. Patients with cluster headache also show structural changes³⁸ in the hypothalamus, and electrical stimulation of the inferior hypothalamus offers clinical improvement in such patients.^{39,40} Findings from a PET study in ten patients with cluster headache with an implanted deep-brain stimulator system showed that hypothalamic stimulation during the headache-free period resulted in significant increases in rCBF in the hypothalamus, ipsilateral thalamus, insular cortex, contralateral primary somatosensory cortex, and anterior cingulate cortex.⁴¹

Chronic nociceptive pain

If we exclude the studies on nociceptive pain with an unknown pathophysiology (low-back pain, fibromyalgia, etc), there are surprisingly few brain-imaging reports on chronic nociceptive pain processing. Two early PET studies on pain responses in patients with rheumatoid arthritis and in post-dental extraction pain are methodologically flawed because of a small study sample and huge differences in age and sex between patients and control groups, and therefore are difficult to interpret.^{21,22}

Neuropathic pain

A number of studies have investigated the cerebral response pattern to painful, usually allodynic, stimulation in a nerve-injured territory. For a control site nearly all studies have used stimulation of the homologous, healthy, contralateral side. All published series have methodological shortcomings, which hamper an unequivocal interpretation of the data. First, because of the heterogeneity in pain location, different body areas have been stimulated across patients, thereby reducing the chance to find activation in brain areas with a somatotopic organisation.^{10,11,13,15} Second, these studies have used patients who differ widely in

their cause of pain, duration of pain, and level of ongoing spontaneous pain.^{10–15} More importantly, these studies have used the homologous contralateral body area as the control site. Unilateral nerve damage is known to be able to cause substantial changes in contralateral sensitivity.^{42,43}

Peyron and colleagues¹⁰ showed that cold allodynia in patients with Wallenberg syndrome was associated with increased activity in contralateral ventroposterior thalamus, primary somatosensory cortex, inferior frontal gyri, and inferior parietal lobule. The authors concluded that allodynia is associated with abnormal responses in the lateral pain pathways. A more recent study from the same group¹¹ assessed brain responses to cold and tactile allodynic stimulation in a large but heterogeneous group of patients with neuropathic pain of mixed peripheral and central origin. Results showed that both forms of allodynia recruit novel responses in the ipsilateral primary somatosensory cortex, secondary somatosensory cortex, and insula, but are not associated with enhanced responses in the thalamus and the anterior cingulate cortex. The data from a study in six syringomyelia patients¹⁴ are in sharp contrast with those by Peyron and colleagues.¹¹ Whereas cold allodynia produced a brain activation pattern close to that of normal cold pain in healthy patients, brush-evoked allodynia did not activate the insula and the anterior cingulate cortex. Petrovic and colleagues¹² studied five patients with peripheral neuropathic pain. Brushing of the allodynic area provoked bilateral increases in rCBF in the thalamus and secondary somatosensory cortex, the contralateral primary somatosensory cortex, anterior cingulate cortex, right anterior insula, brainstem, and cerebellum. Using a similar study design, Witting and co-workers¹³ showed that brush-evoked allodynia in patients with peripheral neuropathic pain activates the orbitofrontal cortex, a structure with extensive connections with limbic and mesencephalic structures, which can induce analgesic effects on electrical stimulation.⁴⁴ As in the Peyron study,¹¹ allodynia was associated with a preponderance of ipsilateral responses in the secondary somatosensory cortex and insular region. Schweinhardt and colleagues¹⁵ tried to separate allodynic pain from spontaneous pain in a group of eight patients with neuropathic pain of peripheral origin.¹⁵ They reported that the perceived intensity of allodynic pain correlates with the size of the activity in the caudal anterior insula. Maihofner and co-workers⁴⁵ studied hyperalgesic responses in patients with complex regional pain syndrome (CRPS), mainly CRPS type 1, in different anatomical areas. A difference with previous studies is that CRPS type 1 does not involve obvious deafferentation of primary afferent input⁴⁶ and therefore the brain-imaging results cannot be affected by deafferentation-induced cortical reorganisation. Hyperalgesia compared with non-painful mechanical stimulation of the homologous non-affected side was

associated with increased responses in the primary somatosensory cortex, secondary somatosensory cortex, contralateral anterior and ipsilateral posterior insula, and prefrontal and posterior parietal cortices. A more recent study from the same group⁴⁷ examined brush-evoked allodynia in 12 patients with CRPS type 1 with a rather homogeneous anatomical distribution of pain complaints. Allodynia ratings correlated with blood-oxygenation-level-dependent (BOLD) signal changes in the contralateral primary somatosensory cortex, secondary somatosensory cortex, posterior parietal cortex, bilateral anterior and posterior insula, and posterior part of the anterior cingulate cortex. A recent fMRI study²³ investigated responses to noxious thermal stimulation in the orofacial region in eight patients with burning-mouth syndrome, a syndrome that could have underlying neuropathic components. Compared with age and sex-matched controls, patients showed greater signal changes in the right anterior cingulate cortex but smaller signal changes in thalamus, prefrontal cortex, and cerebellum. Pain-induced brain activation volumes were also reduced in patients, which suggests that brain hypoactivity could be associated with the pathophysiology of this syndrome.

An important issue concerns the contributing factor of pain to the cortical reorganisation caused by lesions of the peripheral nervous system. There is ample evidence that lesions of peripheral nerves lead to extensive reorganisation at spinal, thalamic, and cortical level.^{48–51} MEG results further suggest that the amount of cortical reorganisation in the primary somatosensory cortex is positively correlated with the presence of phantom pain in amputees⁵² and that analgesic interventions abolish this reorganisation.^{53,54} In patients with CRPS type 1, the shrinkage of cortical maps in primary and secondary somatosensory cortices contralateral to the affected limb in response to non-painful electrical stimulation is paralleled by impaired tactile discrimination.^{55–57} Behavioural training decreased persistent pain, improved tactile discrimination, and restored cortical maps in response to non-painful stimulation.⁵⁶

Receptor-binding studies

Brain-imaging studies investigating changes in BOLD or rCBF only provide indirect measures of neuronal activity. With PET receptor binding studies, it is possible to probe into the neurochemical changes in response to an acute or a chronic pain condition. With respect to pain, the opioidergic and dopaminergic neurotransmitter systems have been investigated.

The dopaminergic system

There is much evidence for a role of forebrain dopaminergic systems in pain and analgesia.⁵⁸ Electrophysiological studies have revealed dopamine-mediated inhibition of nociceptive activity in the

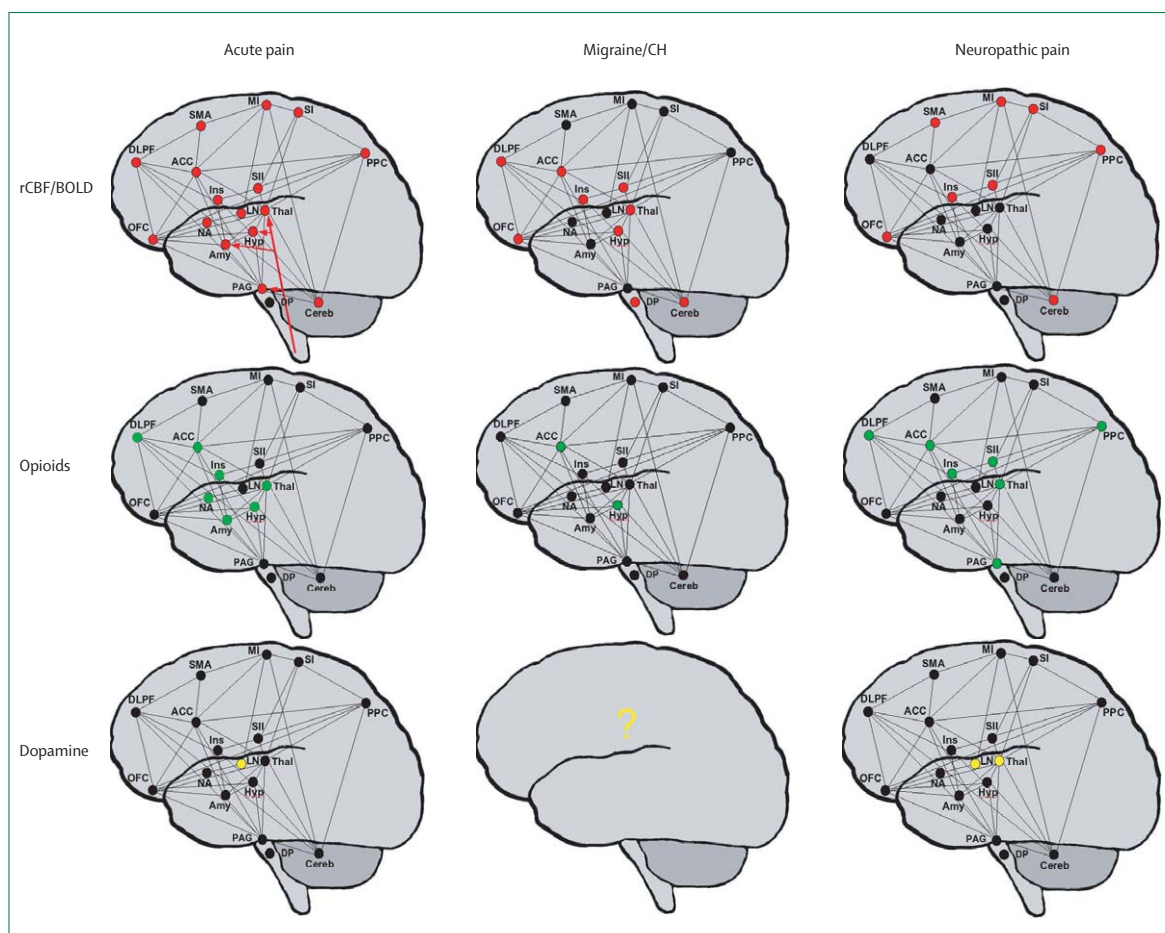


Figure 2: Summary of brain imaging findings for acute pain, migraine-cluster headache, and neuropathic pain

Upper row shows the brain areas showing increased rCBF or BOLD response (indicated in red) in the three pain conditions. The red arrow in the acute-pain condition represents supraspinal areas receiving spinal nociceptive input. Pain-induced changes in opioid binding are indicated in green, pain-induced changes in dopamine binding in yellow. Black circles refer to brain areas showing no pain-induced changes. Black lines show corticocortical connections between different areas within the pain-matrix.^{2-7,10-12,19,23-27,29-38,41,45,47,51-54,56,63-73} SI=primary somatosensory cortex. SII=secondary somatosensory cortex. PPC=posterior parietal cortex. DLPF=dorsolateral prefrontal cortex. OFC=orbitofrontal cortex. SMA=supplementary motor cortex. ACC=anterior cingulate cortex. Ins=insula. Thal=thalamus. LN=lenticular nuclei. NA=nucleus accumbens. Amy=amygdala. Hyp=hypothalamus. PAG=periaqueductal grey. DP=dorsal pons. Cereb=cerebellum. MI=primary motor cortex.

thalamus⁵⁹ and the spinal cord dorsal horn.^{60,61} The D2/D3 receptor antagonist carbon-11-labelled raclopride is a popular PET tracer for studying the striatal dopaminergic system. Striatal ¹¹C-raclopride uptake is very sensitive to changes in synaptic dopamine concentrations,⁶² although extrastriatal changes are difficult to identify with this radiotracer. A study in healthy volunteers showed that cold pain was inversely correlated with D2-binding potential in the right putamen and that cold pain tolerance was inversely correlated with D2-binding potential in the right medial temporal cortex.⁶³ Additionally, the amount of increase in the heat-pain threshold by concurrent cold pain was positively correlated with dopamine binding in the left putamen, which suggests that people with a few available D2 receptors in the forebrain have a high tonic level of pain suppression but a low capacity to recruit dopaminergic pain inhibitory systems after a noxious

conditioning stimulation. The problem with this study is that baseline dopamine binding and not pain-induced dopamine release was measured and hence only shows an indirect relation between striatal D2-dopamine binding and pain responsiveness. By use of fluorodopa, a marker for presynaptic dopaminergic function, Jaaskelainen and colleagues⁶⁴ reported a significant decrease in binding in the right putamen of patients with burning-mouth syndrome, indicating decreased dopaminergic inhibition in this chronic-pain disorder. This study does not allow pathophysiological inferences to be made about burning-mouth syndrome since pain-free individuals were used as controls, as opposed to patients with other pain disorders. A later study showed increased ¹¹C-raclopride binding in the left putamen in disorders of atypical facial pain.⁶⁵ Together, these studies suggest that disorders of chronic facial pain are associated with alterations in the dopaminergic system.

However, since patients suffering from atypical facial pain or burning-mouth syndrome often have psychiatric illnesses, alterations in dopaminergic function could be related to an underlying psychiatric or stress-related response rather than to pain per se.

The opioidergic system

The two PET tracers that have been most widely used for labelling the opioidergic system are carbon-11-labelled carfentanil and carbon-11-labelled diprenorphine. Whereas carfentanil is a selective mu-opiate receptor agonist, diprenorphine binds equally well to mu, delta, and kappa opioid receptors. Experimentally induced sustained pain in healthy volunteers decreases ¹¹C-carfentanil^{66–68} and ¹¹C-diprenorphine⁶⁹ binding in the thalamus, hypothalamus, amygdala, nucleus accumbens, anterior cingulate cortex, and the insular and prefrontal cortices. Jones and colleagues⁷⁰ studied six patients with trigeminal neuralgia before and after successful pain treatment. Compared with the chronic-pain state, the pain-free state was associated with increased ¹¹C-diprenorphine binding in the prefrontal, insular, perigenual, and mid-cingulate cortices, basal ganglia, and thalamus bilaterally, which suggests an increased occupancy of opioid receptors in these areas during trigeminal pain. An alternative explanation is that chronic pain downregulates opioid binding sites. A later study from the same group reported reductions in ¹¹C-diprenorphine binding in the medial pain system in patients with post-stroke pain.⁷¹ In line with this, Willoch and colleagues⁷² showed significantly reduced ¹¹C-diprenorphine binding in the contralateral thalamus, secondary somatosensory cortex, insula, anterior, and posterior cingulate cortices, prefrontal cortex, and midbrain periaqueductal grey matter in patients with central post-stroke pain. Both studies, however, included small patient populations, which varied largely in terms of age, pain history, anatomical site of the brain lesion, and pain distribution. Additionally, whether the

reductions in opioid binding are due to the presence of chronic pain or are the mere consequence of brain tissue loss is difficult to discern. A control group with post-stroke patients without chronic pain is therefore necessary. Finally, a study in patients with cluster headache reported decreasing opioid receptor availability depending on disease duration in the anterior cingulate cortex and hypothalamus.⁷³ Figure 2 summarises the changes in rCBF and BOLD and opioid and dopamine binding in acute pain, migraine and cluster headache, and neuropathic pain disorders.

Measurement of the brain's response to clinical pain

Although PET, fMRI, and MEG have provided important and novel information about the role of the human cerebral cortex in pain processing, they also have important limitations. For instance, excitatory and inhibitory activities are difficult to differentiate with these techniques, although use of sophisticated fMRI approaches can overcome this difficulty.⁷⁴ Additionally, they are non-specific with respect to the underlying neurochemical changes. Third, we do not know whether the same association exists between haemodynamic and metabolic responses in chronic-pain disorders. In recent years, a number of new brain-imaging techniques have been developed, which have proven their use and validity in various other conditions, but which have been only sparsely applied in the pain area.

Proton magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (H-MRS) techniques use an approach similar to classic MRI imaging to measure the concentrations or synthesis rates of neurotransmitters such as glutamate, glycine, and GABA.⁷⁵ Only a few H-MRS studies on pain have been published so far. Mullins and colleagues⁷⁶ showed experimental pain-induced glutamate release in the anterior cingulate cortex, which correlated with subjective pain ratings. Glutamate is an important mediator in normal and pathological pain transmission.⁷⁷ Grachev and colleagues⁷⁸ reported a selective reduction in N-acetyl aspartate and glucose in the dorsolateral prefrontal cortex but not in other brain regions in patients with low-back pain. More recently, Siddall and co-workers⁷⁹ discriminated with high accuracy between patients with chronic low-back pain and control patients using spectra obtained from the anterior cingulate cortex, thalamus, and prefrontal cortex.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is an MRI technique that allows in-vivo study of anatomical connectivity in the human brain.⁸⁰ The technique has been used successfully to show changes in white-matter structure and connectivity after stroke, in neuropsychiatric disorders, and in neurodegenerative diseases.⁸¹ So far,

Panel 2: Methodological difficulties in design of brain-imaging studies in chronic pain

- Difficulty in finding a homogeneous population of chronic-pain patients.
- Difficulty in discerning pain-related from psychological-related effects.
- Possible confound by differences in genetic constitution.
- Difficulty in dissociation of deafferentation-related from pain-related changes in brain activation patterns.
- Homologous contralateral area is not an unbiased site for non-painful control stimulation.
- Difficulty in switching pain on and off in a very precise and time-locked manner.
- Effects of therapeutic interventions could be difficult to dissociate from pain-related effects.

only one case report has been published on a patient with post-stroke pain, showing a reduction in the amount of thalamocortical fibres ipsilateral to the stroke side.⁸² A DTI study in healthy patients showed anatomical connectivity between the periaqueductal grey matter and the prefrontal cortex, the amygdala, the thalamus, and the hypothalamus.⁸³ Hopefully, future studies will combine DTI with fMRI or MEG in chronic-pain disorders and possibly provide important information about changes in anatomofunctional associations within the pain matrix.

Voxel-based morphometry

Voxel-based morphometry (VBM) is a computational approach that measures differences in local concentrations of brain tissue through a voxel-wise comparison of multiple brain images.⁸⁴ VBM allows for comprehensive measurement of differences in specific structures and throughout the entire brain. A selective higher grey-matter density in the hypothalamus ipsilateral to the side of the cluster headache attacks was shown in patients with cluster headache compared with age-matched controls.⁸⁸ The area of increased grey-matter density overlapped with the area showing increased rCBF during a cluster-headache attack, suggesting parallel structural and functional changes. A 5–11% reduction in global cortical grey-matter density was reported in patients with chronic back pain compared with a matched control group, correlating with pain duration.⁸⁵ Additionally, regional grey matter was reduced bilaterally in the prefrontal cortex and in the right thalamus, which was strongly related to pain characteristics. The question remains to what extent these changes are typical for chronic pain conditions. For instance, chronic back pain without relevant cause identified by CT or MRI might be induced by depression, and comparable reductions in grey-matter density have been reported in bipolar depression⁸⁶ and chronic fatigue.⁸⁷

Transcranial magnetic stimulation

PET and fMRI studies do not allow inferences to be made about the functional role of activated areas. This is however possible with the combined use of transcranial magnetic stimulation (TMS) with PET or fMRI. When a TMS coil is placed over the skull, the underlying cortical area can be temporarily inactivated, creating a transient reversible brain lesion.⁸⁸ The strength of the combined PET and TMS or fMRI and TMS approach is that it allows temporary inactivation of a particular brain area showing an increased rCBF or BOLD response to a painful stimulus. If the area inactivated by TMS is functionally involved in pain, this should result in TMS-induced perceptual changes. For instance, rapid TMS of primary motor cortex abolishes capsaicin-induced pain in healthy patients, reduces pain-induced activations in the medial prefrontal cortex, and increases anterior cingulate cortex and supplementary motor area activity.⁸⁹

TMS can also be used to study changes in cortical excitability in chronic pain.⁹⁰

Study of non-experimental forms of pain

From a methodological point of view, the study of non-experimental forms of pain poses far greater challenges. We will address some of these issues in more detail (panel 2).

Switching pain on and off

Whereas in experimental studies pain can be switched on and off in a very systematic and timely manner, enabling use of multiple and randomised pain and pain-free blocks, this is difficult or impossible to accomplish in clinical pain conditions. Therefore, patients are usually scanned on two different occasions in which the painful and pain-free conditions are temporally separated. Since the duration of the therapeutic effects is not always known or may be too long, the timing of the pain and pain-free scans pose some serious difficulties. As a solution, many authors prefer to start with the pain-on condition and do the pain-free condition next.^{17–20,91} This approach raises the problem that scans cannot be randomised and that analgesia-independent timing effects could explain some of the observed changes.⁹² Analgesic interventions also produce effects unrelated to their analgesic action, which could bias brain-imaging results. For instance, an epidural block will not only relieve the pain but will also block the sensory input from a whole-body region, which in itself will lead to massive changes in cortical organisation.⁹³ An alternative approach is to induce an allodynic or hyperalgesic response in chronic-pain patients. This raises the problems that differences in spontaneous pain might affect the stimulus-induced allodynic responses and that stimulation might affect spontaneous pain.

Differences in pain distribution and pain history

Whereas in experimental studies the pain stimulus can be applied in a standard manner to the same body area in all patients, it is difficult to find patients with pain in the same anatomical region. This will affect brain-activation patterns in regions with a known somatotopic organisation, such as the primary somatosensory cortex, secondary somatosensory cortex, and thalamus. An additional complication is that patients commonly vary in terms of pain duration. For instance, Fukumoto and co-workers⁹⁴ showed an inverse association between thalamic blood flow and duration of pain complaints in patients with CRPS type 1.

Pain coping strategies, top-down modulation, and personality

Psychological factors such as anxiety, stress, catastrophising, and pain coping co-determine levels of pain experienced.⁹⁵ These factors are likely to play an

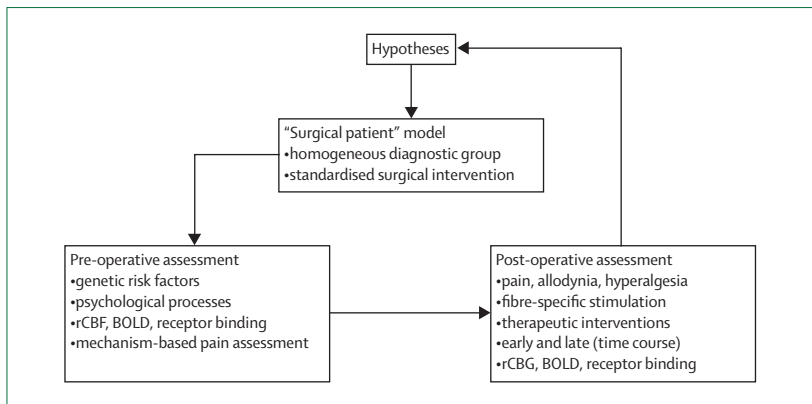


Figure 3: Surgical-patient model and future strategies for the study of central-brain mechanisms in chronic pain

even more important part in longer-lasting pain conditions.⁹⁶ Following prolonged pain states, patients can become depressed and may change their physical and social behaviour, making it extremely complicated to find an appropriate control group. Another complicating factor is that pain patients not only change life-style and behaviour patterns but also often use several other concomitant treatments.

Genetic differences

There is now ample evidence that genetics is a factor at the basis of interindividual differences in pain.^{97,98} Research from our and other laboratories has shown that a patient's response to a suprathreshold pain stimulus predicts with a relative high certainty the development of postoperative pain after surgery.^{99–101} Brain-imaging studies revealed that high pain responders show significantly stronger BOLD responses and activate a larger set of brain areas than do low pain responders.¹⁰² There is also evidence for genetically based differences in pain-induced activation of the mu-opioid receptor system.¹⁰³ This finding has important implications for parallel-group designs comparing pain patients with a group of age and sex-matched controls. Pain-evoked group differences are not necessarily associated with abnormal processing due to the chronic pain condition per se but could be the result of genetic differences between controls and patients with chronic pain. A methodological problem in studies of gene polymorphisms associated with neurotransmitters that are both pain modulatory and vasoactive is that they might interfere with the haemodynamic response function.¹⁰⁴

Post-operative pain as an alternative pain model

The only way to circumvent most of the problems outlined above is to use repeated-measure, prospective-study designs in which homogeneous groups of patients are investigated before and after a standard and well-

described surgical intervention. This approach should include detailed quantitative sensory testing, genetic assessment of risk factors for the development of chronic pain, assessment of psychological functioning, and brain-imaging responses to painful stimulation (figure 3). Of course, only a few patients will develop chronic pain after a surgical intervention, but which of them are at high risk for doing so can be tested preoperatively.^{99–102} Hence, the post-operative pain model has the advantages that the purported onset of the pain can be predicted and that patients can be preselected on the basis of their response to an acute pain stimulus before the surgery. In this way, groups of patients can be selected on the basis of their propensity to develop acute and chronic post-operative pain. The fact that both the low and high-risk patients undergo the same experimental surgical procedure allows the study of time by group interactions. Additionally, homogeneous groups of patients can be studied. Data from classic brain-imaging studies can be supplemented by gene analysis, allowing study of the role of genetic factors in altered brain responses of patients who will develop acute and chronic post-operative pain. Various surgical procedures with a high risk of inducing nerve injury might be followed by a persistent chronic-pain state.^{105,106} Thus, about 10% of patients undergoing inguinal hernia repair develop a chronic-pain syndrome,^{107,108} as do about 30% of patients undergoing mastectomy,^{109,110} 20–40% of patients undergoing thoracotomy,¹¹¹ and 50% of patients after lower-leg amputation.¹¹² Planned surgical interventions could therefore represent an optimum clinical model to study risk factors including brain mechanisms for developing and maintaining a chronic-pain state and where most evidence suggests the pain to be of neuropathic origin.¹⁰⁵ In this context, preoperative and early post-operative brain-imaging studies to a well-defined nociceptive stimulus could be done to lend support to the hypothesis of early post-injury neuroplastic changes, as have been repeatedly shown in experimental studies¹¹³ but never verified in human studies. The exception is perioperative wound hyperalgesia and allodynia, which might not necessarily correlate to intensity of acute or chronic postoperative pain.¹¹⁴

Prospective studies as outlined above offer the additional advantage that they allow for the preoperative assessment of psychological risk factors in the development of post-operative pain. For instance, chronic pain and depression are often comorbid, but whether the depressive symptoms are a consequence of the chronic-pain state or whether a depressive personality trait contributed to the development of chronic pain is difficult to establish. By use of the post-operative pain model, patients can be tested for psychological functioning before the development of chronic pain. Finally, prospective studies in well-defined patients' populations offer a unique opportunity to

Search strategy and selection criteria

References for this review were identified from the authors own files and by searches of PubMed, HubMed, and Scopus with search terms "brain imaging", "PET", "fMRI", "MEG", "chronic pain", "postoperative pain", "neuropathic pain", "migraine", and "headache". Only original research and review papers published in English have been included. There were no date limitations, and the last search was done in August, 2006.

study the mechanisms of interventional, pharmacological, and other therapeutic approaches.

Selective stimulation of Adelta and C-fibres

Heat stimulation through peltier-based contact thermodes is commonly used but has important drawbacks. Since the temperature rise with these systems is generally slow, the peripheral and central neuronal responses are asynchronous. The slow skin absorption of contact heat energy makes heat transfer unpredictable. More importantly, these systems not only activate small myelinated Adelta and unmyelinated C-fibres but also low-threshold mechanosensitive afferent fibres, which can modulate the spinal transmission of nociceptive and thermal information. The use of CO₂ lasers, which operate in the far infrared range (10.6 μm), avoids most of these problems.¹¹⁵ Temperature ramps are extremely fast allowing activation of nociceptors within a few milliseconds. Skin absorption is close to 100% and energy remains confined to the upper layers of the skin where nociceptors are located. CO₂ lasers offer the additional major advantage that they allow stimulation of selectively small myelinated and unmyelinated fibres without concomitant activation of Abeta fibres or selectively C-fibres without Adelta fibres.¹¹⁵⁻¹¹⁸ In this sense, the CO₂ laser offers an invaluable tool to investigate the role of specific fibre classes in post-surgical injury hyperalgesia and allodynia and brain-imaging responses. An example could be brain-imaging verification of an altered Abeta-fibre response in the post-surgical state as suggested in experimental studies.¹¹⁹ A disadvantage of high-power laser stimulation is that because of its highly synchronised fast onset it feels different from most naturally occurring pains. Additionally, its advantages disappear when sustained heat stimuli are needed.

Conclusion

Brain-imaging studies of experimental pain have changed substantially over the past decade. Whereas the first studies tried to do an inventory of the areas activated by a noxious stimulus, recent studies used sophisticated study designs aimed at answering hypothesis-driven questions. In this Review we have

pointed out that the specialty of brain imaging of pathological pain still awaits such a renaissance. Interpretation of the results of most of the published reports is hampered by the use of patients who vary largely in terms of pain pathology, pain distribution, pain history, age, etc. In our opinion, the postoperative pain model circumvents many of these shortcomings. It has the great theoretical appeal that it allows prospective long-term follow-up studies to be done, including a pain-free preoperative assessment of the patient. This model therefore allows the respective roles of the multiple processes, such as genetic constitution, and the role of nerve injury and personality that all contribute to altered brain circuitry in pathological pain to be disentangled. We also argue for a multidisciplinary approach, combining classic rCBF and BOLD-based approaches for brain activation with other techniques, such as genetic analysis, brain-receptor mapping, brain spectroscopy, transcranial magnetic stimulation, and voxel-based morphometry techniques. Finally, the combination of brain-imaging techniques with a high temporal resolution, such as MEG, with pain-stimulation techniques that allow selective stimulation of specific nerve fibre classes is particularly appealing.

Contributors

RK made the general outline for the review, including the figures. HK developed the idea of the postoperative pain model for brain imaging studies. RK and HK drafted the paper and did the literature search.

Conflicts of interest

We have no conflicts of interest.

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