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Neuroimaging: visualising the brain in pain

Abstract The neuroimaging of experimental and clinical pain has revolutionised our understanding of the physiological responses to pain and paved the way for a better understanding of the pathophysiology of chronic pain syndromes. Extensive research on the central mechanisms regarding the sensory-discriminative dimensions of pain have revealed a complex network of cortical and subcortical brain structures involved in the transmission and integration of pain, the so-called pain matrix. Although brain imaging and pharmacological studies have generated some insight into the circuitry that may be involved in the generation of chronic pain symptoms, further research into brain imaging of chronic pain is clearly warranted. However, modern neuroimaging suggests that the chronification of pain (and headaches) involves functional and structural plasticity of both the central and peripheral nervous system.

Key words Pain · Functional imaging · Morphometry · Chronification · Pain matrix PET · MRI · VBM

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Introduction

Brain imaging of pain is largely dominated by experimental acute-pain research. Very little has been done regarding brain imaging in chronic pain. Insight into the fundamental physiology of these syndromes has been limited by the lack of methods available for visualising the pathophysiological background of, for example, headache and possible causes. Functional neuroimaging of patients has, however, revolutionised this area and provided unique insight into some of the most common maladies in man.

Functional neuroimaging in experimental pain

To understand the possible impact of functional studies in primary headache such as migraine and cluster, a clear understanding of the neuroimaging pattern of activation in experimental pain is needed. While clinical and experimental studies can show interactions between the intensity of pain sensation, pain unpleasantness and emotions associated with reflection and behaviour, brain imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (f-MRI) have unravelled pain transmitting structures (the nociceptive system), which include the ascending spinal pathways and a central network of brain structures. The spinal pathways converge onto the brain stem, thalamic nuclei, limbic cortical structures (amygdala, hypothalamus, insular cortex, anterior cingulate cortex (ACC)) and the sensorimotor cortices. Activation of the ACC has been repeatedly reported in PET studies on the sensation of somatic or visceral pain and attributed to the emotional response to pain [1–4]. Insula activations appear in studies involving application of heat [2, 5, 6], subcutaneous injection of ethanol [7], somatosensory stimulation [8], and during cluster headache [1] and atypical facial pain [9]. Given its anatomical connections,

the insula is viewed as a relay station for sensory information into the limbic system, along with its role in the regulation of autonomic responses [10]. The thalamus is a site where activations would most be expected in the acute pain state. Activation of the contralateral thalamus due to pain is known from experimental animals [11] and functional imaging studies in humans [2, 4]. The ability to locate pain plays a pivotal role in immediate defence and withdrawal behaviour. It is therefore no surprise that the primary somatosensory cortex (SI) shows a clear somatotopic organisation ipsi- and contralaterally to painful stimulation. Furthermore, differential representations of hand and foot stimulation appear within the contralateral opercular–insular region of the secondary somatosensory cortex (SII) [12, 13]. This result provides evidence that both SI and SII encode spatial information of nociceptive stimuli without additional information from the tactile system and highlights the concept of a redundant representation of basic discriminative stimulus features in human somatosensory cortices [13]. Functional imaging has also been able to demonstrate that a very basic form of spatial coding – that of stimulus laterality of pain stimuli – is not only preserved in target regions of the afferent neuraxis such as thalamus, SI, SII and posterior insula [12, 14], but also in subcortical structures of the motor system, such as the putamen, red nucleus and cerebellum [13]. This indicates that on a behavioural level, relevant nociceptive information is processed in the basal ganglia and made available for pain-related motor responses [15].

The above-mentioned central network of brain structures involved in pain transmission and processing, the so-called 'pain matrix', is under dynamic top-down modulation (so called antinociceptive system) by brain mechanisms that are associated with anticipation, expectation and other cognitive factors. Figure 1 outlines the above-mentioned regions generally activated in functional imaging studies on pain.

Functional neuroimaging in clinical pain

Unlike the abundant research available on experimental pain [16–18], only a few studies using functional imaging (PET or f-MRI) have investigated clinical pain [19–25] and the results of these studies are incongruent [26]. One of the reasons is that it is difficult to assemble a homogenous patient cohort with exactly matched symptoms, duration of disease, medication history, age distribution, etc. [27]. However, studies have begun to evaluate CNS changes that occur in patients with neuropathic pain [28–30], phantom pain [31–33], post-herpetic neuralgia [34], chronic back pain [35], fibromyalgia [36, 37], irritable bowl syndrome [38] and complex regional pain syndrome [22, 39]. However, unlike in primary headache syndromes such as migraine [24] and cluster headache [40], functional imaging has not yet provided reproducible findings specific to the disease or, the ultimate goal, a pathophysiological basis for these syndromes. Certainly more work and longitudinal studies are warranted to investigate the natural course of pain diseases and to track pharmacological effects to gain a better understanding of acute pain and pain control.

Functional neuroimaging in behavioural responses to pain

The nociceptive system is essential for reacting to potentially life-threatening situations. As such the brain mediates a response to a complex situation, which may not consist of only the pain stimulus itself. Pain is unpleasant and contains emotional feelings involving contextual and cognitive factors, because pain often occurs within a situation that is threatening and stressful. These 'cognitive' qualities and reactions to a situation involving pain have had an immense impact in pain research using functional imaging. Based on these investigations, it has been proposed that two principal ascending spinal pathways for pain exist: the 'lateral' and the 'medial' spinothalamic tract or pain system. The lateral pain system consists of the ventroposterior lateral (VPL) nucleus of the thalamus and the primary and secondary somatosensory cerebral cortical areas (S1 and S2) and is believed to be involved in discriminative sensory pain transmission. The so-called 'medial pain system' consists of the cingulate cortices, amygdala and hypothalamus and, following this theory, processes the emotional and somatic responses to pain (e.g. affective-motivational components) [41–43]. This "classic model" however, does not imply that the sensory and affective dimensions of pain are interrelated and that these dimensions can be modulated by cognitive factors.

Functional imaging has begun to reveal the neural circuits involved in the modulation of pain experience. Central neural mechanisms associated with such phenomena as placebo, hypnotic suggestion, attention and distraction are thought to have an effect on pain perception by modulating neural activity within many of the brain structures shown in Figure 1. This modulation includes endogenous pain-inhibitory and pain-facilitation pathways that descend to the spinal dorsal horn. One of the key players is the ACC, as it is not only involved in the actual perception of pain but also in imagined pain experience [44], and observation of another human receiving a pain stimulus [45]. It should be pointed out that directing attention away from a painful stimulus is known to reduce the perceived pain intensity and results in decreased activation of ACC subregions responsive to painful stimulation [46–48]. The placebo response in pain seems to be mediated at least in

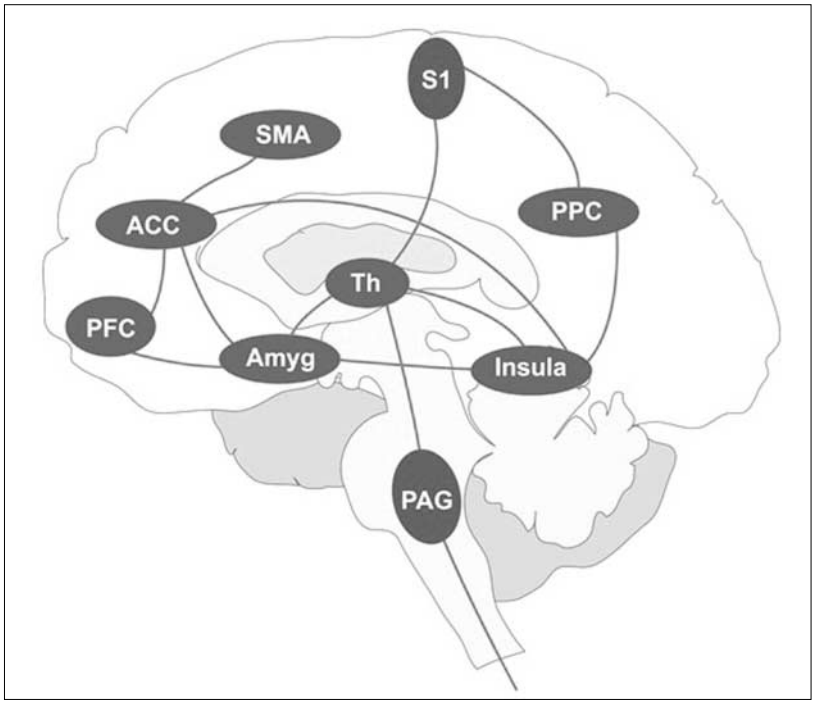

Fig. 1 The pain-matrix consists mainly of the thalamus (*Th*), the amygdala (*Amyg*), the insular cortex (*Insula*), the supplementary motor area (*SMA*), the posterior parietal cortex (*PPC*), the pre-frontal cortex (*PFC*), the cingulate cortex (*ACC*), the peri-aqueductal grey (*PAG*), the basal ganglia and cerebellar cortex (*not shown*) and the primary (*S1*) and secondary (*S2, not shown*) sensory cortex. For review see [16, 17]

part by the ACC [49–52] and the same holds true for the response to hypnosis and pain [53–55].

Neuroimaging in headache

Migraine

In several PET studies in patients with migraine without aura [24, 56–58], significantly higher rCBF values were found during the acute attack compared to the headache-free interval in brainstem structures over several planes. These structures lay towards the midline and their localisation has been refined to the dorsal pons [24, 59]. Increased activation was also found in the inferior anterocaudal cingulate cortex, as well as in the visual and auditory association cortices during the attack, but was not detected in these areas in the interval scan or after relief from headache- and migraine-related symptoms through treatment [56].

The consistent increases in rCBF in the brainstem persisted, even after sumatriptan had induced complete relief from headache, nausea, phonophobia and photophobia. This increase was not seen outside the attack. It can be concluded that the observed activation was unlikely to be just the result of pain perception or increased activity of the endogenous anti-nociceptive systems. Very recently, these findings have been replicated and significantly extended. It seems clear now that the brainstem activation is indeed highly specific to migraine, but ipsilateral to the pain and at a slightly different location [24, 58]. Interestingly, the same area was found to be activated in chronic migraine, which was treated using suboccipital stimulation [60]. It is certainly beyond the resolution of the PET scanner to attribute foci of rCBF increases to distinct brainstem nuclei. However, dysfunction of the regulation of brainstem nuclei involved in anti-nociception and extra- and intracerebral vascular control provides a comprehensive explanation for many of the facets in migraine [11, 61]. The importance of the brainstem for the genesis of migraine is underscored by the presence of binding sites for specific anti-migraine compounds within these structures [62]. The only direct clinical evidence for the brainstem as primum movens in migraine was reported by Raskin et al. in non-headache patients who developed migraine-like episodes after stereotactic intervention with lesioning of the PAG and more specifically the DRN [63]. Interestingly, these headaches responded to specific serotonergic agonists.

Medication overuse headache

Recently, 16 migraine patients suffering from medication overuse headache were investigated using 18-FDG PET (measuring glucose metabolism) before and 3 weeks after medication withdrawal and compared to a control population. Before withdrawal, the bilateral thalamus, orbitofrontal cortex, anterior cingulate gyrus, insula/ventral striatum and right inferior parietal lobule were hypometabolic, while the cerebellar vermis was hypermetabolic [64]. Following withdrawal of analgesics, all areas but the orbitofrontal cortex

showed an almost normal glucose uptake. The authors suggested that medication overuse headache may be associated with reversible metabolic changes in pain processing structures like other chronic pain disorders, but also with persistent orbitofrontal hypofunction. Interestingly, the latter is known to occur in drug dependence, which may predispose subgroups of migraineurs to recurrent analgesic overuse.

Trigeminal autonomic cephalalgias

The group of trigeminal autonomic cephalalgias comprises cluster headache, paroxysmal hemicranias and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome) [65]. The concept of trigeminal autonomic cephalalgias signifies a possibly shared pathophysiological basis for these syndromes that is not shared with other primary headaches, such as migraine or tension-type headache [66]. Thus far, findings in functional imaging of primary headache syndromes have been specific to the disease [67, 68], suggesting that these techniques may be helpful in unravelling the degree of congruence between clinically analogous headache syndromes. Neuroimaging has made substantial contributions in recent years to understanding these relatively rare but important syndromes [40, 69–71]. These studies consistently show that significant activations ascribable to the acute headache attack were observed in the ipsilateral hypothalamic grey matter when compared to the headache-free state. In contrast to migraine [56], no brainstem activation was found during the acute attack compared to the resting state. This is remarkable, as migraine and cluster headache are often discussed as related disorders and identical specific compounds, such as ergotamine and sumatriptan, are currently used in the acute treatment of both types of headache [72]. Moreover, no hypothalamic activation was seen in experimental pain induced by capsaicin injection into the forehead [73]. This is important because injection into the forehead would activate first (ophthalmic) division afferents, which belong to the trigeminal division predominantly responsible for pain activation in cluster headache. These data suggest that while primary headaches such as migraine and cluster headache may share a common pain pathway – the trigeminovascular innervation – the underlying pathogenesis seems to differ significantly, as can be inferred from the different patterns of clinical presentation and responses to preventative agents [72].

Regarding cluster headache, these findings prompted the use of deep brain stimulation (DBS) in the posterior hypothalamic grey matter in several patients with intractable CH headache and led to a complete relief of attacks [74–76], some with a follow-up of more than four years [76, 77]. In order to unravel the brain circuitry mediating stimulation-induced effects, a very recent study applied PET in hypothalamic deep brain stimulated patients and found that stimulation induced both activations and deactivations, which are situated in cerebral structures belonging to neuronal circuits usually activated in pain transmission and notably in acute cluster headache attacks. These data argue against an unspecific antinociceptive effect or pure inhibition of hypothalamic activity. Instead, the data suggest a hitherto unrecognised functional modulation of the pain processing network as the mode of action of hypothalamic DBS in cluster headache [78].

Morphometric studies in pain

Recent neurobiological research suggests cortical reorganisation on a functional level as a consequence of chronic pain [79]. This "functional reorganisation" was not only detected in patients suffering from phantom limb pain [33], but also in chronic back pain patients [35]. The extent of functional changes in patients suffering from chronic regional pain syndrome (CRPS Typ I) correlated highly with the intensity of pain and the magnitude of mechanical hyperalgesia [22, 39]. Apart from functional plasticity in chronic pain states, few studies have addressed the issue of structural reorganisation [80]. Using voxel-based morphometry, a whole-brain technique that is capable of discovering subtle, regionally specific changes in grey matter by averaging across subjects, a significant change in the structure of the brain has been reported in several chronic pain states including chronic back pain [81, 82], chronic tension-type headache [83] and phantom limb pain [84]. As the adult human brain may change its structure in response to environmental demands [85, 86], the central question arises of whether these findings of cortical morphological alterations may be a consequence of chronic pain, or contribute to the neurobiological basis of the chronification of pain, or both.

Regarding episodic pain syndromes, only migraine [87, 88], tension-type headache [83] and cluster headache [89] have been reported to show structural brain changes when compared to healthy volunteers. Interestingly, in cluster headache, a co-localisation of morphometric and functional changes was achieved by using two different imaging techniques that could separately identify a highly specific brain area previously considered on clinical and biological grounds to be involved in the genesis of the cluster headache syndrome [90]. The structural data show a morphometric change of the neuronal density in this region, whilst the functional imaging data are related to the neuronal activity in this area. Together, they demonstrated for the first time the precise anatomical location in the central nervous system responsible for cluster headache. Furthermore, given that this area is involved in circadian rhythm and sleep–wake cycling [91], these data suggest an involvement of this hypothalamic area as a primum movens in the acute cluster attack.

Outlook

Insight into the fundamental physiology of pain and chronification of pain is mandatory if we are to treat these syndromes effectively. However, our knowledge is hampered by a scarcity of studies on clinical pain (whereas a vast number of studies on experimental pain exist), and furthermore, the results of these studies are incongruent. As repeated measures design is warranted, the post-operative pain model is highly appealing to gain a better understanding of acute pain and pain control. The combination of functional and structural imaging and the multimodal imaging approach in which classic brain-activation studies are supplemented with other imaging modalities (VBM, DTI, MR-Spectroscopy etc.) as well as correlation of these data with electrophysiological, genetic and biochemical findings are clearly essential.

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