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Imaging pain: a potent means for investigating pain mechanisms in patients

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Editor's key points

- Neuroimaging can improve our understanding of pain mechanisms, analgesic action and the placebo effect.
- New modelling approaches can explore the dynamic processes influencing pain perception.
- Neural mechanisms of the effects of personality and expectancy on pain perception and analgesia have been explored.
- Future developments will continue to expand our knowledge of pain mechanisms, allowing translation from laboratory to clinic.

Summary. Chronic pain is a state of physical suffering strongly associated with feelings of anxiety, depression and despair. Disease pathophysiology, psychological state, and social milieu can influence chronic pain, but can be difficult to diagnose based solely on clinical presentation. Here, we review brain neuroimaging research that is shaping our understanding of pain mechanisms, and consider how such knowledge might lead to useful diagnostic tools for the management of persistent pain in individual patients.

Keywords: chronic pain; neuroimaging, magnetic resonance imaging, functional

Pain is an unpleasant sensation that is associated with, or described in terms of, a bodily injury.[1] Clinicians have long regarded pain as a symptom or warning of disease that should be investigated to expedite treatment of pathology. Unfortunately, medicine does not yet possess every cure, or indeed knowledge of every pathophysiology that can generate pain. Pain can persist despite the best efforts of physicians. Chronic pain is currently defined by the duration of physical symptoms but is, in reality, suffering strongly associated with feelings of anxiety, depression, and despair.[2]

In the individual, chronic pain is highly influenced by disease pathophysiology, psychological state, and social milieu. The pathogenesis of chronic pain syndromes is often unclear. Research continues to suggest specific patho physiologies that may distinguish between different chronic pain syndromes, for example, fibromyalgia, complex regional pain syndrome. Whether these clinical syndromes can be distinguished as diseases in their own right with specific treatments, or considered as a collection of symptoms that are driven by shared mechanisms, remains unclear. Regardless, psychosocial factors can supervene to influence how pain is perceived or reported by patients, and these factors can operate unconsciously. Their contribution to the chronic pain state further determines appropriate and holistic management of the patient. Hence, there is a desperate need for additional methods that can quantify disease load or psychosocial contributions to the chronic pain state in patients.

In the fifth century BC, Hippocrates declared that pain, like all consciousness, must emerge from brain activity.[3] Robust scientific evidence for that philosophical intuition arrived much later (two decades ago) with the demonstration of increased and localized brain activation during pain in humans.[4] We now accept that pain may be caused by bodily injury, but as a consciousness, must be generated in the brain.

Functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetoencephalography (MEG), and scalp electroencephalography (EEG) are commonly used to study the neural bases of pain. Researchers are also increasingly using other magnetic resonance-based measures (e.g. diffusion tensor imaging, spectroscopy, and volumetric imaging) to assess pain-related changes in the brain's wiring, chemistry, and structure in order to gain further insights into the neurobiology of pain, particularly chronic pain. There are excellent reviews written recently to summarize the findings of neuroimaging studies in healthy individuals and in patients.[5 6] Here, we focus on recent neuroimaging studies that continue to shape our understanding of pain in health, disease, and illness. We review the progress in neuroimaging research that is contributing to the development of clinically relevant tools for the management of pain in patients.

The pain 'neuromatrix'

Neuroimaging studies have now identified several cortical regions in humans that are considered to be important for the perception of pain. The primary and secondary somatosensory cortices (insular and anterior cingulate) and the prefrontal cortices (PFCs) are commonly activated, often bilaterally, and during painful experiences. Furthermore, altered activity in subcortical areas (e.g. brainstem periaqueductal grey (PAG), hypothalamus, amygdala, hippocampus, and cerebellum) is also

observed during pain. Thus, activity within several diverse regions of the brain seem to be necessary for the multidimensional experience that is pain.[7–9] Some of these regions comprise the so-called 'pain neuromatrix',[10] a term that is often misused, in which multiple inputs are processed to produce an output (neurosignature) that is bespoke for an individual depending on context, mood and cognitive state.[8] Hence, pain is the product of a widely distributed and variably accessible neural network in the brain, rather than an inevitable consequence of noxious stimulation. Current research suggests that parts of this network can be accessed by non-nociceptive events or inputs to produce 'pain-like' experiences (e.g. during empathy for others,[11] romantic rejection,[12] and social exclusion).[13] Hypnotically induced pain in susceptible individuals[14] and central post-stroke pain are further examples that illustrate the latent capacity of the brain to elicit pain without concomitant peripheral nociceptive inputs.

Remarkably, none of the brain regions identified above is uniquely associated with pain; they are also involved in many other sensory, motor, cognitive, and emotional functions. Some regions within the so-called pain neuromatrix exhibit significantly correlated activity with sensory or emotional descriptions of the painful experience, suggesting that they have a significant role in pain generation but no brain region has been shown to be exclusively activated during pain experiences.[15–18] Disruption of the specific regions within this pain matrix by cortical lesions very rarely remove or 'numb' pain completely.[19 20] Surgical cingulotomies, performed for intractable pain syndromes, may reduce emotional or motivational aspects of the clinical pain state but leaves intact the capacity for nociceptive pain.[21] In fact, prior failure to associate cortical activity or cortical lesions to the experience of pain had encouraged the view that pain had little true cortical representation.[22 23] These observations suggest that there is no critical or fixed brain region for pain.

Despite extensive research, an area of the brain that is analogous to the primary visual cortex (i.e. 'primary pain cortex') has not been identified. To date, there is no pattern of brain activity indicating pain in an individual with absolute certainty for use by medical, legal, or other regulatory bodies. For example, 'pain-related' brain activity from noxious stimulation can occur in patients in minimally conscious states[24] but such activations do not necessarily prove pain perception in these individuals. Nonetheless, they suggest that the neuroanatomical substrates for pain are functionally intact and raise the possibility of pain in these uncommunicative subjects with obvious clinical implications.

Imaging nociception

Nociception is defined as the 'neural process of encoding noxious stimuli'. Although nociception is neither necessary nor sufficient for pain, it is required for protective autonomic or reflexive responses that are essential for our survival. Nociceptors are peripheral sensory neurones which are evolved to respond specifically to high-intensity environmental stimuli that threaten the physical integrity of the organism.[25] The neurobiology of these first-order afferents is arguably better understood compared with central neurones onto which they project to transmit information to the brain.[26]

Investigators have attempted to trace the flow of nociceptive information by examining the temporal sequence of brain activations evoked by noxious stimulation. In humans, the earliest intra-cortical electrical potentials that are evoked by noxious laser stimuli applied to the hand occur simultaneously within the posterior insular region and mid-cingulate cortex.[27 28] These regions receive nociceptive input via spino-thalamocortical pathways and are thought to provide a primary interoceptive representation of the physiological condition of the body.[29] Activation of the posterior insula during nociception in humans has been shown to be somatopically organized.[30] The importance of the posterior insula for nociceptive pain is further suggested by functional imaging studies of pain empathy,[11] hypnotically induced pain,[14] and recalled pain experiences.[31 32] Neural activations during such pains may be similar to that of physically induced pain but there is often attenuation of activation within the posterior insula when pain is reported in the absence of nociceptive stimulation.[14] Researchers from independent groups have shown that direct electrical stimulation of the posterior insular region can lead to painful sensations being reported.[33 34] The same does not appear to be true of other cortical regions that are also considered part of the pain neuromatrix.[23 34] Additionally, the insular cortex has been identified as the most consistently activated region during pain that is induced by nociceptive stimuli.[9] These converging data suggest that the posterior insular region might represent a critical neural node through which nociceptive information must be processed. Hence, a 'nociceptive cortex' within the operculo-insula region may be postulated, akin to other major senses.

Brain dynamics

As discussed above, the experience of pain requires activity within various regions of the brain. Nevertheless, how pain arises from the flow of information between these different brain regions is largely unknown, as investigating this phenomenon requires a multimodal approach, of which few published studies exist.[35] Most studies involve EEG or MEG alone, which record brain activity with high temporal resolution but relatively poor spatial resolution when compared with fMRI. A human scalp EEG study of cortical potentials evoked by highly noxious stimuli has revealed that late, rather than early, laser-evoked responses are associated with conscious detection of noxious stimuli.[36] Hence, the consciousness of pain appears to emerge at later stages of such processing when neural information is being integrated across multiple cortical regions.

The processes by which the brain prioritizes nociceptive information over competing sensory stimuli for conscious awareness should also be examined.[37] This may explain how the perception of pain arises from nociceptive input. Synchronous neuronal oscillations at gamma-band frequency (>40 Hz) are known to occur when the relevant sensory stimulus is selected for neural representation and perception.[38] Using MEG, Gross and colleagues[39] demonstrated that painful laser