

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.

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 pathophysiologicals 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

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.

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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 individuals¹⁴ 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 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 states²⁴ but such activations do not necessarily prove pain perception in these individuals. Nonetheless, they suggest that the neuro-anatomical 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 somatotopically 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 colleagues³⁹ demonstrated that painful laser

stimuli were associated with stronger gamma-band oscillations (GBO) than unperceived stimuli of equal stimulus intensity, suggesting that the perception of pain emerges when nociceptive input is prioritized in the brain. A more recent EEG study further revealed that, unlike evoked potentials, GBO is not suppressed with repetitive noxious (laser) stimulation.⁴⁰ In that study, healthy subjects perceived and reported that repeated stimuli were just as painful as the original stimulus. However, the laser-evoked potentials tended to diminish in amplitude with each stimulus repetition. Hence, these potentials appear to signal the novelty, rather than the intensity, of pain experienced.⁴¹ Repetition suppression does not occur with GBO; this observation lends further support for the role of GBO in determining the emergence of pain from a noxious stimulus.

Dynamic causal modelling and structural equation modelling are analytical methods that have the potential to further our understanding of pain. These techniques use data from EEG, MEG, fMRI, or PET studies to investigate brain dynamics and cortical coupling,^{42–44} and are now being applied in the field of pain.⁴⁵ Such analyses take us beyond a simple spatial representation of pain towards a network-based understanding of this condition that better reflects the dynamic nature of the pain experience.

Prefrontal-limbic control

Numerous imaging studies demonstrate that the PFC can regulate the perception and behavioural expression of pain in humans. The PFC is reciprocally connected to limbic regions and these connections form the neural substrates through which the motivational-emotional aspects of pain can be regulated. The belief that pain from noxious stimulation can be controlled increases tolerance of such painful stimuli; this analgesic effect involves the ventrolateral PFC.⁴⁶ Individuals can be taught to reinterpret the significance of adverse events so that the negative emotional responses (e.g. fear) can be controlled. During successful reappraisal, the dorsolateral PFC engages the nucleus accumbens and suppresses amygdala activation.^{47–48} Reducing the fear associated with impending pain via extinction learning requires activation of the ventromedial PFC.^{49–50} However, anxiety levels can increase if extinction learning fails to lower such fear,⁵¹ which can exacerbate a pain experience via para-hippocampal mechanisms.^{52–53}

Frontal-limbic regions are reciprocally connected to the brainstem. This neuroanatomical connection presents another route through which pain can be controlled—via inhibition of neurones within the spinal cord that transmit nociceptive information to the brain. Distraction from pain has been shown to involve activity within the cingulo-frontal cortex, thalamus, and PAG^{54–55} and, more recently, suppression of spinal cord activity.⁵⁶ Likewise, placebo analgesia invokes and alters activity in similar regions within the central nervous system.^{57–59}

The brainstem integrator

Neurones in the spinal cord that transmit information regarding noxious events to higher centres within the brain receive

descending control from supraspinal regions. This powerful modulatory input, emanating from the frontal-limbic regions, is integrated within the rostral ventromedial medulla (RVM) and PAG; activity within these regions in the brainstem determines whether the nociceptive information is prioritized.⁶⁰ Depending what the situation demands, these brainstem regions co-ordinate the inhibition or facilitation of nociception. Classical ‘fight or flight’ responses engage immediate inhibitory effects for survival in battlefield or success in competitive sports. After retreat, the same brainstem network can facilitate nociception if physical injuries are sustained. Heightened sensitivity to noxious stimuli (hyperalgesia) is protective during recovery, promoting tissue healing.

Hyperalgesic states

We have demonstrated that, in healthy volunteers, the mesencephalo-pontine reticular formation (MPRF), which projects to the RVM, regulates the expression of hyperalgesia in different central sensitization states. For example, cutaneous capsaicin initiates central sensitization by activation of peripheral nociceptors. The result is hyperalgesia and its maintenance involves MPRF activity.⁶¹ Cessation of remifentanyl, a potent i.v. opioid can also induce^{62–64} hyperalgesia.^{65–66} This opioid-induced phenomenon was investigated in a combined psychophysical-fMRI study.⁶⁴ MPRF activation was significantly increased only in hyperalgesic subjects and correlated negatively with the degree of hyperalgesia suggesting that brainstem activity regulates the behavioural expression of central sensitization during opioid withdrawal.

Personality and pain

The degree to which limbic and brainstem regions are functionally linked by neural activity can explain the influence of personality on pain thresholds. Using fMRI, we found that insular-brainstem functional connectivity⁶⁷ was weaker in more anxious individuals, who also had lower pain thresholds when compared with less anxious individuals.⁶⁸ Hence, the influence of personality traits on pain can be substantiated by mechanisms involving the descending control of pain; therefore, an anxious and pain-vigilant personality might arise from less effective intrinsic regulation of nociception.⁶⁹

Expectancy effects

Individuals often ‘get what they expect’ from any treatment for pain. Expectancy is often used to explain the placebo effect which is now substantiated by neuroimaging research as a genuine psychobiological event. Mechanisms for placebo analgesia operate within the neural circuit for the descending control of pain which include the ACC, PAG, and the spinal dorsal horn.⁵⁹ More recently, we investigated whether effects from positive and negative expectancies of opioid analgesia engaged similar brain regions in healthy subjects.⁷⁰ The experiment involved a fixed and constant infusion of remifentanyl. Subjects reported slightly lower pain compared with baseline when the infusion commenced but knowledge of that was hidden. Pain relief became significantly superior when subjects

were told that the infusion had commenced. When informed that the infusion had ceased (though in reality the infusion was continued), their ratings of pain returned to baseline. The fMRI data revealed that effects of positive and negative expectancies on opioid analgesia involve *distinct* neuroanatomical substrates. Expectation of poor analgesic effect was accompanied by activation of the entorhinal cortex, the hippocampal region that mediates the exacerbation of pain through anxiety⁵² and inhibition (negative activation) of the perigenual ACC (pgACC). Conversely, positive expectation of analgesic effect was associated with increased pgACC activation, suggesting the descending mechanisms of pain inhibition were engaged.

In our study, activations within the primary somatosensory, insular, and mid-anterior cingulate cortices followed subjective reports of pain, with the intensity modulated by expectancy using a fixed remifentanyl dose. However, activations in these same regions also correlate with pain modulated by varying doses of remifentanyl without psychological manipulations. This raises important questions about whether innate placebo mechanisms in the brain might be altered fundamentally by the presence of the active opioid. Atlas and colleagues⁷¹ used a full factorial experimental design in their recent study to investigate potential interaction effects between remifentanyl and expectation on pain ratings and also brain activity. They did not find significant interaction effects on pain ratings or brain activity. Pain relief from remifentanyl and expectation were indistinguishable based on subjective pain ratings. fMRI did not reveal regions where interaction effects were significant. Instead, expectancy and remifentanyl effects were distinguishable because they influenced different brain regions. Additionally, expectancy and remifentanyl effects had different onsets. Expectancy effects occurred soon after the subjects became aware the infusion had started, whereas remifentanyl effects

become prominent only after peak blood concentrations were achieved from the infusion. These studies on drug and expectancy effects suggest that expectancy effects possess distinct functional neuro-anatomies. Further research is needed to explore the possibility of isolating the contribution of placebo or nocebo effects on pain based on neuroimaging data from clinical drug trials.⁷⁰

The brain and chronic pain

Neuroimaging research in patients with chronic pain have revealed altered structure, function, and neurochemistry in the frontal-limbic-brainstem regions compared with healthy controls underscoring the importance of this descending neuro-circuit for the regulation of pain in humans.

Converging evidence suggests that frontal-limbic dysfunction accompanies chronic pain (Fig. 1). Early fMRI studies have shown altered functional activation of PFC by noxious stimuli in patients with chronic pain. Both hypo-activity^{72–74} and hyperactivity of the PFC^{75–77} have been observed. Further evidence of frontal-limbic dysfunction in chronic pain states comes from PET-ligand studies which suggests abnormal opioidergic transmission within frontal-limbic regions in patients with chronic pain (e.g. complex regional pain syndrome,⁷⁸ central post-stroke pain,^{79 80} and fibromyalgia).⁸¹

Numerous investigators have used voxel-based morphometry (VBM) to demonstrate subtle but distinct alterations in grey-matter densities in the brains of patients with chronic pain when compared with healthy controls. Distinct grey-matter changes have been observed in the prefrontal^{82–84} and limbic regions^{85–88} in disparate chronic pain syndromes. However, these MR-based changes do not necessarily imply neuronal loss. Furthermore as these MRI data are from cross-sectional studies in patients, they cannot reveal whether the chronic pain

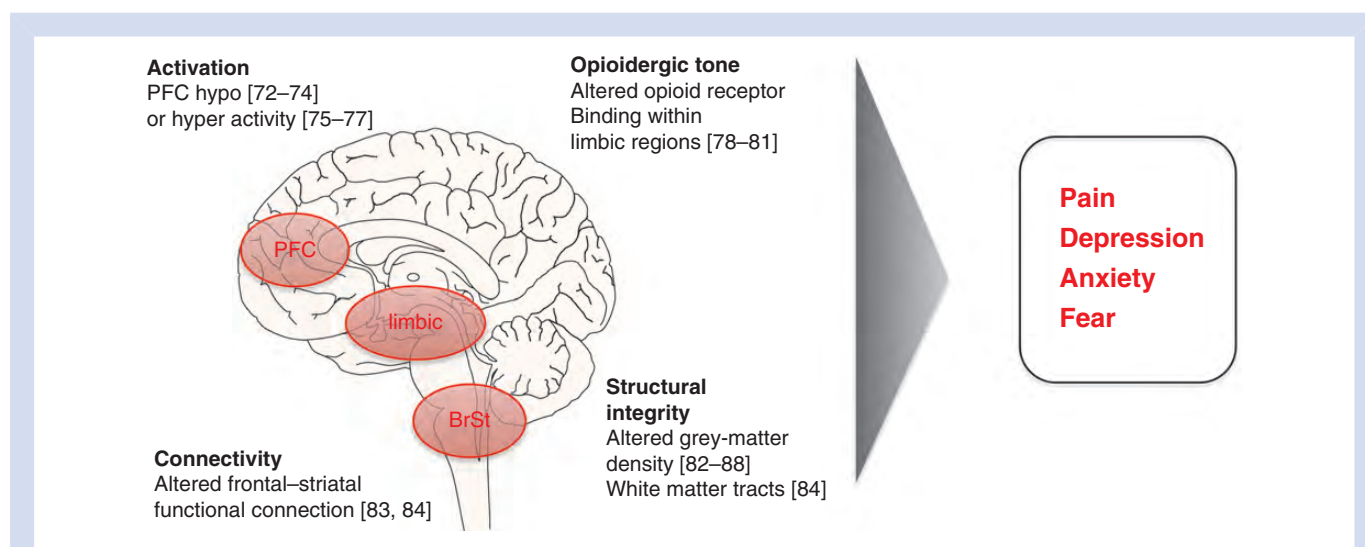


Fig 1 The PFC-limbic-brainstem (BrSt) pathways is involved in the descending modulation of pain. Brain imaging studies (references in brackets) have revealed altered functional activation, structure and neurochemistry of prefrontal and limbic regions in association with symptoms reported by patients with chronic pain.

state is the cause or consequence of regional grey-matter changes. Nonetheless, in rodent models of neuropathic pain, neuronal remodelling,⁸⁹ and altered MRI-based measures of grey-matter structures⁹⁰ occur in the frontal-limbic regions and correlate with 'anxiety-like' behaviours after the peripheral nerve lesions. These animal data suggest that the brain can change as a consequence of aberrant input from damaged nociceptive afferents and potentially contribute to the state of chronic pain.

Longitudinal VBM studies in patients with chronic pain now suggest that abnormalities in grey-matter densities within specific brain regions can resolve with improvement in

symptoms.^{91–93} These data have been extended to changes in cortical *thickness* which is a more quantitative measure that can be compared between studies, unlike grey-matter densities.⁹⁴ Seminowicz and colleagues demonstrated that the dorsolateral PFC thickened in patients with chronic lower back pain who reported improved symptoms. Additionally, the degree of thickening correlated with the extent of clinical improvement. Interestingly, when compared with controls, patients whose symptoms improved still had thinner cortices in the DLPFC, though the difference did not reach statistical significance. This finding may well reflect incomplete recovery of the pain state in that patient cohort. However, it prompts us to

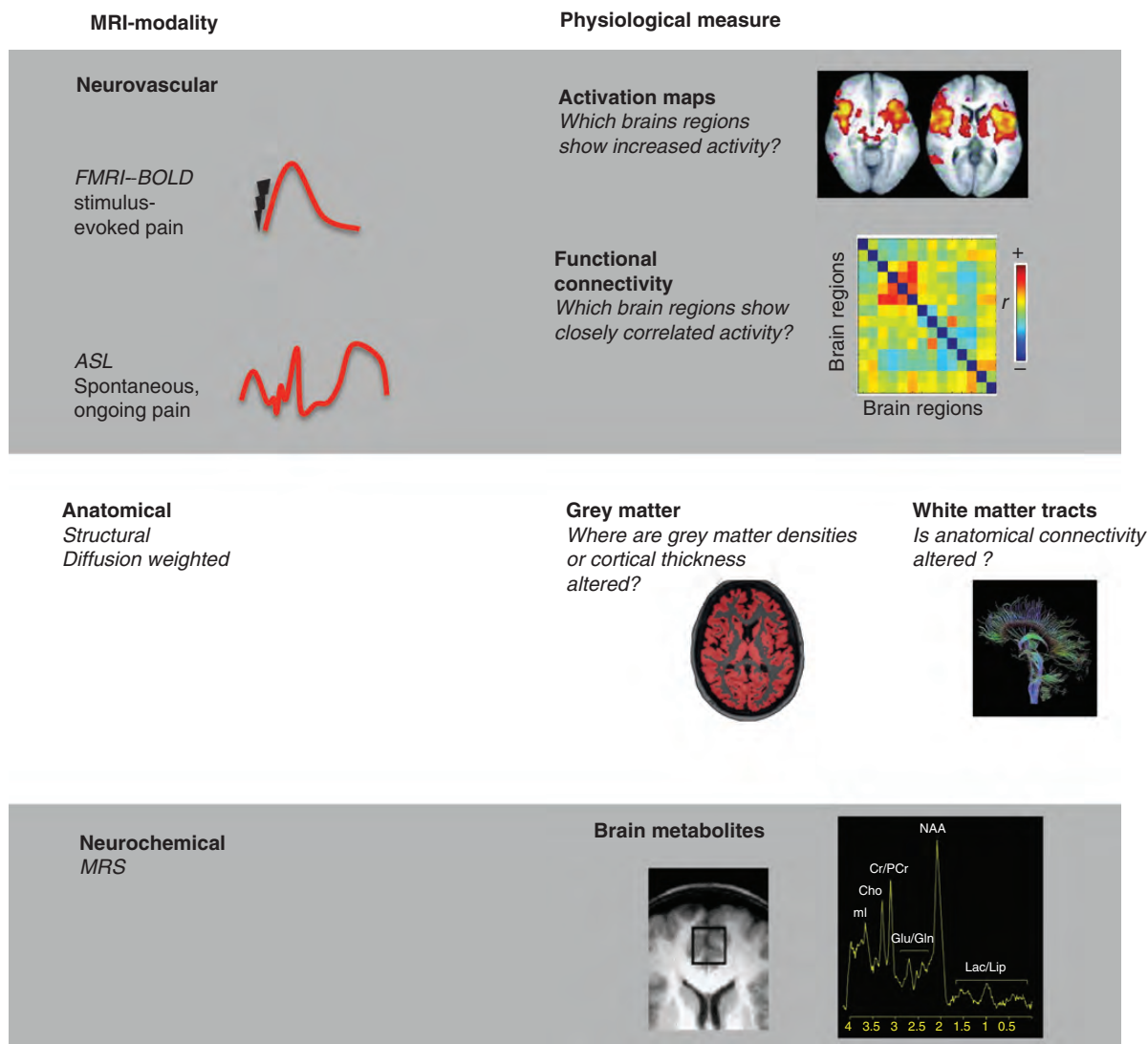


Fig 2 MRI-based imaging modalities that measure the brain function, structure, and neurochemistry. Blood oxygenation level dependent (BOLD) fMRI and ASL techniques can map the brain's neurovascular responses that are associated with pain symptoms. These techniques reveal where activation or cerebral perfusion is altered within the brain. More sophisticated connectivity analyses provide information regarding the flow of neural information within the brain. Advanced analyses of anatomical MRI scans can demonstrate subtle changes of grey-matter densities or alterations in the connectivity of white-matter tracts between brain regions. Magnetic resonance spectroscopy quantifies changes in brain metabolites to reveal potential areas of neuroinflammation or neurodegeneration.

consider whether predisposition to chronic pain can be predicted based on prefrontal structure or function.

The longitudinal fMRI study by Baliki and colleagues⁸³ demonstrated the value of cortical-striatal connectivity in predicting the 1-year outcome of patients with sub-acute back pain. Greater functional connectivity between the PFC and nucleus accumbens predicted pain persistence suggesting that the frontal-striatal connection is involved in the transition from acute to chronic pain. Cortico-striatal connectivity is known to sub-serve a number of neuropsychological functions and is increased during cognitive reappraisal of emotions,⁴⁷ a skill that may be relevant for coping with chronic pain. Hence, the increased frontal-striatal Fc observed in patients 'destined' for chronic pain could represent an adaptive mechanism that was eventually overwhelmed.

Brain dynamics

In recent years, fMRI has revealed that the brain exhibits highly correlated spontaneous and slow (<0.1 Hz) oscillatory activities, even in the absence of any sensory stimulation.⁹⁵ The biological significance of these 'resting' state networks is still unclear.⁹⁶ It has been suggested that incoming sensory stimulation sculpts the activity and temporal dynamics of these spontaneous networks, reducing the variability of their fluctuations, to allow stable patterns of neural firing within cortical regions that are associated with stimulus perception.⁹⁷ For example, baseline fluctuations in fMRI activity can influence whether pain arises from noxious stimulation.^{68 98}

Our ability to detect, analyse, and determine changes in the brain's resting state networks (RSNs) has improved considerably in recent years. The default-mode network (DMN) is one such RSN and includes the medial PFC, medial temporal lobes, posterior cingulate cortex, and retrosplenial cortex.⁹⁹ Studies utilizing fMRI or PET have shown that patients with chronic pain can have abnormal patterns of intrinsic brain activity in the DMN.^{77 100 101} These studies indicate that resting brain activity within various brain regions is associated in some way with spontaneous pain in this condition.

Activity in the various brain regions that make up the DMN is highly correlated when an individual 'rests with eyes closed' and does not perform any explicit task. Hence, the DMN is often associated with 'mind-wandering' which philosophical and contemplative traditions believe is associated with unhappiness, in contrast to 'living in the moment'.¹⁰² Meditation is associated with relative deactivation of the main nodes of the DMN (medial prefrontal and posterior cingulate cortices) in experienced meditators.¹⁰³ Experienced practitioners also report that pain is less unpleasant during meditation. Their subjective reports were associated with decreased activation in PFCs but increased activation in the sensory regions, including the posterior insular.^{104 105} These observations suggest neural mechanisms that underlie 'pain modulation' by meditation comprise increased sensory processing and decreased cognitive control, and contrast with established neural mechanisms for descending control of pain. Such mechanisms may explain the efficacy of psychological approaches that

integrate meditative practice and cognition-based therapy for the management of chronic pain.¹⁰⁶

The future

MR-based brain imaging methods are developing rapidly (Fig. 2). Using quantitative arterial spin labelling (ASL), we are now able to measure regional changes in cerebral blood flow that can be associated with tonic, rather than phasic neural events.^{107–109} This non-invasive technique provides an absolute measure of cerebral perfusion and provides us with the opportunity to identify the neural correlates that underpin the unrelenting, spontaneous and ongoing pain that is the dominant characteristic of chronic pain syndromes. Spinal cord fMRI is now available and further research is being undertaken to enable simultaneous acquisition of neural activities (spinal dorsal horn, brainstem to the cortex) which, in combination with microneurography,¹⁰² could allow mapping of the entire 'pain-pathway' (nociceptor to brain). Machine-learning algorithms implemented in 'brain-reading' studies provide new opportunities for dissecting the neural bases of pain perception.¹¹⁰ Neuroimaging methods are also being developed as clinical tools that reveal the mechanisms that underlie chronic pain in patients where disease pathophysiology and psychosocial influences on pain are unclear based on clinical presentation alone. The challenge now is to improve the sensitivity and specificity of imaging techniques to allow their development as diagnostic tools for the individual patient in our pain clinics.

Declaration of interest

None declared.

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