Scandinavian Journal of Pain 2 (2011) 108–120

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Review

Review of neuroimaging studies related to pain modulation

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ARTICLE INFO

Article history:
Received 25 November 2010
Received in revised form 17 May 2011
Accepted 18 May 2011

Keywords:
Pain control mechanisms
Nociception
Neuroimaging
PET
fMRI
MEG

ABSTRACT

Background and purpose: A noxious stimulus does not necessarily cause pain. Nociceptive signals arising from a noxious stimulus are subject to modulation via endogenous inhibitory and facilitatory mechanisms as they travel from the periphery to the dorsal horn or brainstem and on to higher brain sites. Research on the neural structures underlying endogenous pain modulation has largely been restricted to animal research due to the invasiveness of such studies (e.g., spinal cord transection, brain lesioning, brain site stimulation). Neuroimaging techniques (e.g., magnetoencephalography (MEG), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)) provide non-invasive means to study neural structures in humans. The aim is to provide a narrative review of neuroimaging studies related to human pain control mechanisms.

Methods: The approach taken is to summarise specific pain modulation mechanisms within the somatosensory (diffuse noxious inhibitory controls, acupuncture, movement), affective (depression, anxiety, catastrophizing, stress) and cognitive (anticipation/placebo, attention/distraction, hypnosis) domains with emphasis on the contribution of neuroimaging studies.

Results and conclusions: Findings from imaging studies are complex reflecting activation or deactivation in numerous brain areas. Despite this, neuroimaging techniques have clarified supraspinal sites involved in a number of pain control mechanisms. The periaqueductal grey (PAG) is one area that has consistently been shown to be activated across the majority of pain mechanisms. Activity in the rostral ventromedial medulla known to relay descending modulation from the PAG, has also been observed both during acupuncture analgesia and anxiety-induced hyperalgesia. Other brain areas that appear to be involved in a number of mechanisms are the anterior cingulate cortex, prefrontal cortex, orbitofrontal cortex and nucleus accumbens, but their exact role is less clear.

Implications: Neuroimaging studies have provided essential information about the pain modulatory pathways under normal conditions, but much is still to be determined. Understanding the mechanisms of pain control is important for understanding the mechanisms that contribute to failed pain control in chronic pain. Applying fMRI outside the brain, such as in the trigeminal nucleus caudalis of the spinotrigeminal pathway and in the dorsal horn of the spinal cord, and coupling brain activity with activity at these sites may help improve our understanding of the function of brain sites and shed light on functional connectivity in the pain pathway.

Contents

DOI of refers to article:10.1016/j.sjpain.2011.05.007.
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1877-8860/$ – see front matter
doi:10.1016/j.sjpain.2011.05.005

1. Introduction

Pain research has advanced greatly since Descartes [1] made the first documented attempt to understand pain. A noxious stimulus was argued to activate the brain and signal pain in a single line-labelled fashion. It is now obvious that pain processing is far more complex. A noxious stimulus does not necessarily cause pain. Nociceptive signals travelling from the periphery to the dorsal horn or brainstem in response to a noxious stimulus are subject to modulation via a number of endogenous inhibitory and facilitatory mechanisms before they transcend to higher brain sites [2]. Dysfunctions in inhibitory control or activation of facilitatory mechanisms may, at least in part, explain chronic pain conditions such as complex regional pain syndrome (CRPS), migraine, fibromyalgia and musculoskeletal pain conditions [3–6]. A thorough understanding of pain modulatory mechanisms may thus be an important step towards developing more effective management. Currently chronic pain conditions are notoriously difficult to manage successfully.

In healthy humans, research into endogenous pain modulation has mostly involved some form of noxious stimulation of the skin, muscle or viscera (e.g., by mechanical, electrical, ischemic, chemical or thermal stimulation, or by subcutaneous or intramuscular injections of pain-inducing or inflammatory compounds such as hypertonic saline, glutamate or capsaicin). Also more invasive techniques, such as rectal balloon distension, have been performed. The neuro-chemical mechanisms underlying pain responses have been investigated by combining such studies with the administration of neurotransmitter/neuropeptide agonists or antagonists and assessing the effects of these compounds on pain perception. Apart from studies on patients with different forms of spinal cord lesions or brain injuries, research on the neural structures underlying pain modulation have largely been restricted to animal research due to the invasive measures available for such studies (e.g., spinal cord transection, brain lesioning, direct brain site stimulation). The emergence of neuroimaging techniques such as magnetoencephalography (MEG), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) has created opportunities to study the neural structures involved in pain modulation in humans. Such work suggests that the thalamus, primary somatosensory cortex (SI), secondary somatosensory cortex (SII), insula, forebrain (e.g., prefrontal cortex), amygdala and anterior cingulate cortex (ACC) are the primary brain sites active during an acute pain experience. Together these areas have come to be termed the 'pain neuromatrix' [7–9], although some debate surrounds the idea of a pain network. The thalamus, SI, SII and the posterior parts of insula are believed to underlie the sensory-discriminatory experience of pain while the amygdala, the ACC and the anterior parts of insula are thought to be involved in the affective-motivational components of pain, and prefrontal cortex (PFC) in the cognitive-evaluative aspect of pain [10]. Additional brain sites may be active depending on the endogenous pain control mechanisms put into play. In particular, the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM) are thought to be involved in descending pain modulation via the so-called PAG–RVM network [11]. This paper describes the current understanding of some of the most studied pain control mechanisms from a neuroimaging point of view. Somatosensory, affective and cognitive factors shape both the quality and the magnitude of the pain experience. The approach taken is to provide a narrative review of specific pain modulation mechanisms within these three domains.

2. Modulation by somatosensory factors

2.1. Diffuse noxious inhibitory controls

Various noxious stimuli (e.g., thermal, mechanical, electrical, ischemic and chemical) have been shown to produce remote analgesia in humans through what has been referred to as the 'pain inhibits pain' principle [12–19]. The effect is usually demonstrated by the inhibition of an initial pain by a second pain placed in an area remote from the initial pain. Animal studies suggest that noxious stimulation inhibits activity in spinal [20–24] and trigeminal wide dynamic range neurons [25–27] located outside the segmental dorsal horn excited by the stimulation. Such effects have been termed diffuse noxious inhibitory controls (DNIC) [28]. In rats, lesion studies have shown that a supraspinal loop [20,23,29], emanating from subnucleus reticularis dorsalis in caudal medulla underlies the response [30–32], and rodent studies have implicated many neurotransmitter systems in the DNIC effect (i.e., serotoninergic, opioidergic, dopaminergic and neurokinergic systems) [33–39].

In humans, only a limited number of studies have investigated the neural structures of DNIC. One fMRI study found decreased activity in pain-related brain sites, such as SI, ACC, PFC and amygdala, during analgesia to electric shock in the right ankle produced by painful cold water immersion of the left foot [40]. The counter-irritation stimulus (i.e., noxious cold water stimulation of the left foot) produced sustained activation in SI, ACC, anterior insula (aINS), PFC, and orbitofrontal cortex (OFC) as well as the midbrain (PAG area) and the pons, consistent with activation of the 'pain neuromatrix' (SI, ACC, aINS, PFC) and descending modulation of spinal nociceptive activity (PAG, OFC) [40]. The reduction of phasic pain activity in ACC, PFC and amygdala during DNIC suggests the release of endogenous opioids at these sites [40,41]. Activity in the ipsilateral OFC was specifically related to the extent of analgesia and covaried with amygdala activity which could suggest a cortico-amygdaloid regulation of opioid release [40,41].

Another study reported bilateral activation of SI, ACC (Brodman area 24′ (BA24) and 32′ (BA32)) and PFC during reduction of pain to rectal balloon distension following a similar cold pressor task [42], consistent with activation of the 'pain neuromatrix'. These areas have connections to the PAG and the RVM [43,44]. Taken together with the previous study, one may thus speculate whether the PAG–RVM network [11] is activated and responsible for the pain reductions seen during DNIC activation. Reduced activation was present in anterior and posterior insula, the medial thalamus and the PAG which, according to the authors, may reflect the promotion of inhibitory feedback loops [42]. Unlike in the earlier study [40], the OFC was not activated.

A recent fMRI study using cold pressor stimulation of the right leg to reduce pain to phasic heat in the left arm also suggests the involvement of the PAG–RVM network [45]. The study found reductions in areas thought to be related to pain perception, such as the right (contralateral) thalamus, bilateral SII, anterior and posterior insula, the cingulate cortex, bilateral amygdala and the medulla, during reduced pain (DNIC). Greater analgesia in the arm correlated with reduced activity in right thalamus, left insula, dorsolateral PFC, and the dorsal part of medulla. Naloxone, an opioid antagonist, reduced the strength of the correlations between analgesia and areas of the insula, dorsolateral PFC and medulla, but did not completely eliminate the correlations. Naloxone also reduced the DNIC activation of SII, amygdala, PAG/midbrain, and the OFC. This, and the finding that naloxone did not affect the subjective experience of pain, suggests that the PAG-opioidergic system plays an *indirect* role in DNIC. Furthermore, the study found enhanced coupling between subgenual ACC (sACC) and the PAG/midbrain, and between sACC and the left amygdala, as well as between sACC and the hypothalamus, and between sACC and the medulla, during DNIC. The strength of the couplings correlated positively with the extent of analgesia, and was diminished by naloxone (for the coupling between sACC and the PAG/midbrain, and the sACC and the left amygdala), suggesting a pain modulatory role of the ACC during DNIC.

Studies on the neural structure of DNIC in humans thus collectively show that, during DNIC, activity in brain areas underlying pain perception is reduced (e.g., SI, ACC, PFC, amygdala, insula, thalamus). The studies furthermore suggest that the PAG–RVM network and the ACC may be involved in producing the remote pain inhibitions. However, as mentioned by some of the authors [45], activation of the PAG and other sites during DNIC scenarios may reflect the simultaneous activation of other pain control mechanisms that are difficult to control for, such as stress-induced analgesia (e.g., the PAG–RVM network [46], see Section 3.4), and attentional shifts (e.g., the ACC [47], see Section 4.2). Furthermore, activation of the caudal medulla, thought to underlie DNIC in animals, was not demonstrated in either of the human fMRI-DNIC studies, possibly because the area of caudal medulla involved in DNIC (the subnucleus dorsalis reticularis) is a very small region difficult to image during fMRI [40]. More research into the neuroanatomical structures involved in DNIC in humans is thus required in order to clarify the role of brain sites in the human DNIC response.

2.2. Acupuncture

Similar to the analgesia produced by noxious stimulation, acupuncture can reduce pain [48]. Whether acupuncture analgesia is more effective than sham acupuncture (i.e., placebo) is, nonetheless, under debate [49,50]. In electrical acupuncture, both stimulation of Aβ-afferents and Aδ-fibers induce analgesia [51], but stimulation of Aδ-fibers appears to produce a more potent analgesic effect [52–54]. Spinal gating, i.e., competition between CNS input from the painful region (i.e., from Aδ- or C-fibers) versus that from non-painful acupoints (carried by Aβ-fibers), may contribute to acupuncture analgesia [55]. C-fiber stimulation additionally plays a role in manual acupuncture probably by activating DNIC mechanisms [27,56]. The role of C-fibers in electrical acupuncture is less clear [57]. Nonetheless, other mechanisms may play a role as DNIC effects are usually short lived (minutes) whereas acupuncture analgesia may peak for hours or days after stimulation [58,59].

Animal and human studies suggest that the primary modulator involved in acupuncture is the central release of opioid peptides [57,60–63]. Serotonin and noradrenaline have also been implicated in the analgesic effects of acupuncture in rodents [64–67]. Despite the central release of such neuromodulators, the analgesic effects of acupuncture are often restricted to the ipsilateral side which has led researchers to suggest that other mediators, such as adenosine A1 receptors located on ascending nerves, play a role in acupuncture analgesia [68].

The many modulators involved in acupuncture analgesia complicate the mapping of central circuits in acupuncture analgesia [69]. Efforts are further complicated by findings from comparative studies in humans which suggest that electrical acupuncture activates different brain sites than manual acupuncture [70], that different brain sites are activated during short versus long term acupuncture [71], and that different acupoints (even within the same spinal segment) activate different, although somewhat overlapping, central mechanisms [72]. Neuroimaging of healthy volunteers have shown that acupuncture increases activity in areas such as the nucleus raphe magnus (NRM—a part of the RVM) and the PAG [73–75]. In addition, brain sites such as the SI, SII, ipsilateral superior frontal gyrus, supplementary motor area, caudal ACC, putamen, insula, contralateral medial and inferior frontal gyri, thalamus, pons, temporal lobe, prefrontal gyrus, occipital cortex, hypothalamus, nucleus accumbens, bilateral cerebellum and primary somatosensory-motor cortex have been found to be active during acupuncture analgesia in humans while regions such as the ACC, the amygdala, PFC, sensory thalamus, and the hippocampus have been found to be deactivated [70,73,76–83]. Thus areas thought to be involved in the sensory-discriminatory aspect of pain (e.g., SI, SII, insula, thalamus), as well as the affective (e.g., amygdala, ACC) and cognitive-evaluative (e.g., PFC) aspects of pain appear to be modulated by acupuncture. In addition, areas involved in pain control (e.g., the PAG and NRM [11]) are activated, suggesting their involvement in acupuncture analgesia. However, an important note is that these complex brain activation/deactivation patterns may be confounded by brain patterns that reflect acupuncture's other therapeutic effects (e.g., nausea and vomit reduction [84], depression reduction [85], weight loss [86], and hypertension regulation [87]).

A study of low versus high frequency electrical analgesia specifically assessed correlations between brain activity and acupuncture analgesia [76]. Activity in contralateral primary motor cortex and supplementary motor area, ipsilateral superior temporal lobe (positive correlations), and bilateral hippocampus (negative correlations) were correlated with 2-Hz acupuncture analgesia, and activity in contralateral parietal BA40, ipsilateral caudal ACC, nucleus accumbens, and the pons (positive correlations) and contralateral amygdala (negative correlations) were associated with 100-Hz acupuncture analgesia [76], suggesting the specific involvement of these sites in the *analgesia* generated by acupuncture. Brain regions that had positive correlations both to 2- and 100-Hz acupuncture analgesia included bilateral SII and insula, and contralateral caudal ACC and thalamus.

Collectively, acupuncture studies thus indicate widespread effects and actions in the brain that are not uniform across studies, possibly because of differences in acupuncture duration, type of acupuncture (e.g., electrical versus manual), and participant expectation and anticipation (e.g., placebo). The effects may furthermore be confused with acupuncture's other therapeutic effects. These factors must be taken into account in future imaging studies of acupuncture in order to provide a clearer picture of the supraspinal sites contributing to acupuncture analgesia. Studies that have looked at the specific association between pain reductions and brain activity suggest the involvement of bilateral SII, insula, caudal ACC and thalamus in acupuncture analgesia, but their exact function is yet to be determined.

2.3. Movement

Most people have experienced that the shaking or movement of a painful body area can relieve acute pain, and motor cortex stimulation has been demonstrated to alleviate chronic pain [88]. However, little is known about the mechanisms underlying these effects. Two different mechanisms have been proposed to account for movement-related pain modulation: modulation by ascending large fiber signals generated by movement in a gating type effect (centripetal) or modulation of somatosensory signals at cortical or subcortical levels by movement-related brain activities in primary and supplementary motor areas (centrifugal) [89,90]. Studies using MEG and somatosensory evoked potentials suggest modulation of painful laser-evoked SI and SII activation by movement [89,91]. Pain intensity evoked by laser stimuli applied to the dorsum of the hand was reduced by ipsi- and contralateral active movement of the hand but not by ipsilateral passive movement [89]. Inhibition of the contralateral SI amplitude was seen following active and passive movement of the ipsilateral hand, and SII activation was attenuated by ipsilateral and contralateral active movements but not ipsilateral passive movements. A later study using somatosensory evoked potentials to painful galvanic stimulation found attenuation of contralateral SI activity with subsequent increases in contralateral SII and posterior cingulate cortex following ipsilateral isometric contraction and attenuation of bilateral SII activity followed by decreases in the SI and ACC following contralateral isometric contraction [91]. Attenuation of LEPs together with attenuation of ACC activity (but not attenuation of SI and SII) was reported before movement takes place in the movement preparatory period [90]. Thus, it appears that activity in brain areas of the 'pain neuromatrix' are reduced immediately before or during movement-induced pain reduction (i.e., ACC, SI, SII). However, to the best of our knowledge, no studies have assessed activity in movement-related brain areas (i.e., at primary and supplementary motor areas) during movement-induced analgesia in healthy humans, nor has any studies assessed competing activity of somatosensory and proprioceptive input to the dorsal horn. Such studies are needed to clarify the mechanisms by which this type of pain modulation occurs.

In relation to the discussion of movement-related gating of pain, it is interesting to note that in patients with central pain following a spinal cord injury (SCI), pain may be evoked by imagined foot movements [92]. Using fMRI, Gustin et al. [92] found that movement imagery evoked signal increases in the supplementary motor area and cerebellar cortex in both SCI subjects and controls. In SCI subjects, it also evoked increases in the left primary motor cortex (MI) and the right superior cerebellar cortex. The activation of the perigenual ACC, right dorsolateral prefrontal, right and left anterior insula, supplementary motor area and right premotor cortex correlated with percentage increase in pain intensity. This suggests that a cognitive task of imagining movement in patients with deafferentation is capable of increasing an ongoing chronic pain and activity in the 'pain neuromatrix' (i.e., ACC, PFC and aINS) by a centrifugal effect independently of peripheral inputs. In contrast to this finding, visual illusions of walking has in other studies in spinal cord injury patients been shown to decrease pain [93,94].

When looking at studies on movement, it is important to consider the pain modulatory effects of attention (see Section 4.2) as more attention will inevitably be focused on the moving limb. To control for attention, studies on evoked potentials and imagined movements have included various control situations (e.g., guided imagery, watching a film or increased attention towards the painful region or stimulation), and, thus, the changes observed seem to be related specifically to movement or movement imagery [92–94].

In summary, studies on pain and movement suggest that movement or imagined movement has the potential to modulate pain and activity in the 'pain neuromatrix' (e.g., the ACC, SI and SII). However, the pain inhibitory effects need to be discriminated from conditions where movement may exacerbate pain, for example musculoskeletal pain conditions. Activity in motor-related brain sites, such as the supplementary motor area and premotor cortex, probably plays a role in the modulation of pain by movement. Future neuroimaging studies should assess activity in movement-related brain sites as well as spinal activity related to movement-induced analgesia to clarify the neural mechanisms by which movement reduces pain.

3. Modulation by affective factors

A range of emotions have also been shown to influence the perception of pain. It is generally recognized that negative emotions increase pain [95–97] whereas positive emotions decrease it [95–99], although the underlying mechanisms in specific emotional states still remain unclear. Neuroimaging studies are especially important in determining the neural structures involved in these mechanisms as animal studies are of limited use due to the nature of affective factors. A growing number of imaging studies on emotional modulation of pain have emerged. Below, the modulation of pain by depression, anxiety, catastrophizing and stress are discussed.

3.1. Depression

Depressive symptoms have been associated with a heightened pain experience [100,101], and depression is a frequent complaint in chronic pain patients [102,103]. Nonetheless, reports also exist of normal or reduced pain sensitivity in clinically depressed patients [104–106]. The mechanism underlying the connection between depression and pain is unknown, but may be explained by a close biological link; in depression, there is a dysfunction in the serotonin and norepinephrine neurotransmitter systems [107], and pain is modulated by serotonin and norepinephrine descending pathways in the spinal cord from the brainstem [108]. Central hyperexcitability and reduced pain thresholds in depressed patients suggest that a lack of central inhibition could underlie both [109].

Neuroimaging studies show that the 'pain neuromatrix' overlaps with the abnormal neural activity structures of patients suffering from depression (e.g., at PFC, thalamus, amygdala, ACC and insula [110,111]. Furthermore, in an fMRI study, depressed patients experienced hyperactivity in the left ventrolateral thalamus, the right ventrolateral PFC and the dorsolateral PFC (areas responsible for the sensory-discriminatory (i.e., thalamus) and cognitive-evaluative aspects of pain (i.e., PFC)) compared to healthy controls when stimulated with a painful 45 °C thermode [105]. Symptom severity correlated positively with activity in the left ventrolateral nucleus of the thalamus, suggesting that depressed patients experience greater 'pain activity' in the brain than healthy people. Using fMRI, Strigo et al. [112] observed that a clinical sample of major depressive disorder patients (MDD) exhibited increased activity in the right amygdala and decreased activity in the PAG, rostral ACC and PFC, compared to healthy controls, during painful stimulation relative to non-painful stimulation. During anticipation of pain, the right aINS, the dorsal ACC, and the right amygdala (areas responsible for the affective-motivational aspect of pain) showed increased activation. This may indicate that depressed patients experience increased emotional processing before they experience pain. The activity in amygdala was also associated with greater levels of perceived helplessness. The increased emotional reactivity of depressed patients anticipating pain may thus cause impaired pain modulation [112]. How the anticipation of pain affects the ability to modulate pain in depressed patients is not clear. Cognitive models of depression propose that depressed individuals are biased in their monitoring of negative information and exhibit a heightened awareness of their interoceptive state [112]. The results of Strigo et al. [112] may represent a neural correlate of hypervigilant monitoring of negative information in MDD. As we describe in Section 4.2, paying attention to painful stimuli may enhance its perceived painfulness.

Other imaging studies similarly hypothesize dysfunctional emotion regulation during the experience of pain in depressed persons [113,114]. In patients with fibromyalgia, Giesecke et al. [114] found that depression did not modulate the sensory dimension of pain processing, as measured by fMRI and QST. However, depression was correlated with increased activity in neural regions (i.e., amygdala, and contralateral aINS) that process the affective dimension of pain. It thus appears that the emotional experience of pain is different for an individual suffering from depression. Using fMRI, Berna et al. [113] investigated the hypothesized dysregulation in healthy volunteers who underwent induction of negative mood and noxious thermal stimulation. In the negative mood state, the participants showed increased activity during pain in insula, thalamus, hippocampus, dorsolateral PFC, OFC, and sACC-areas of the 'pain neuromatrix'. The participants who reported the highest degree of pain unpleasantness during negative mood showed significantly higher activity in the amygdala and the inferior frontal gyrus. These neural structures, underlying emotional regulation of pain, may thus form part of the mechanisms that affect pain processing during depressed mood by enhancing the emotional experience of pain. These data indicate that the modulation of pain by negative mood is not merely a question of biased attentional pain modulation, but a question of impaired emotion regulation.

Imaging studies have thus found depression to be associated with increased activity in some areas of the 'pain neuromatrix' (e.g., the insula, left ventrolateral thalamus, the right ventrolateral PFC and the dorsolateral PFC, amygdala) and decreased activity in others (e.g., rostral ACC, PFC) with some inconsistencies (e.g., increased PFC activity in one study and increased PFC activity in another). In addition, depression may be associated with absent inhibitory descending modulation (e.g., reduced PAG activity). The finding of a link between depression and reduced pain perception in some studies points to the need for further studies. Such differences may relate to the modality of the painful stimulus or differences in chronicity or degree of depression. Imaging studies suggest that the negative mood of depressed individuals impairs pain modulation in neural structures involved in emotion regulation. Especially, the affective elements of pain processing may be sensitive to depressed mood resulting in enhancement of pain affect. Future studies that seek to clarify the underlying mechanisms of the alteration (or dysregulation) of pain by depression, for instance, by incorporating the assessment and treatment of depression and pain simultaneously, are very much needed.

3.2. Anxiety

Another negative emotion that can enhance pain is anxiety [115]. Anxiety, in contrast to fear, involves an undefined future threat without a clear focus [116]. It shares elements with fear (e.g., heightened muscle activity, escape or avoidance behaviour and catastrophizing thoughts), but these are less severe [116]. Hypervigilance (e.g., scanning of the environment for threats, selective attention to threat-related rather than neutral stimuli) forms an important part of anxiety [117]. The brain-gut peptide hormone cholecystokinin (CCK) probably acts like an antagonist to endogenous opioids in mediating the effect of anxiety on pain [118–122]. CCK-driven activation of pro-nociceptive pathways from the PAG and RVM may also underlie anxiety-induced hyperalgesia as CCK evokes activity in animal PAG neurons [123,124] and RVM ON neurons [125]. Part of the anti-opioid activity of CCK also appears to take place in the PAG [126,127].

Consistent with the findings in animals, an fMRI study in humans showed activity in the PAG in environmental situations that induced hyperalgesia during anxiogenic stress [128]. Activity was also observed in the ventral tegmental area (VTA), RVM and parabrachial nucleus. Activity in the VTA and the entorhinal cortex in the anticipatory period before noxious thermal stimulation predicted insula activity during stimulation, consistent with modulation of activity in pain-related brain sites. Ploghaus et al. [129] similarly demonstrated that the entorhinal cortex exhibited a stronger response to anxiety-associated noxious stimuli compared to identical noxious stimuli without associated anticipatory anxiety, and that the enthorhinal areas predicted activity in the closely connected affective (perigenual cingulate) and pain intensity coding (mid-insula) areas. Gray and McNaughton [130] propose that the hippocampal formation (in the enthorhinal cortex) increases pain during anxiety by amplifying signals to the neural representation of the noxious stimulus. In this way, anxiety biases the individual to adapt its behaviour to the worst possible outcome [130]. Also using fMRI, Ochsner et al. [131] found that the more subjects feared pain (indexed by the fear of pain questionnaire), the more activity was seen in the anterior and posterior cingulate and OFC during painful versus non-painful stimulation. High fear of pain may thus increase the sensitivity in regions which encode and evaluate the emotional aspects of pain. Anxiety about the negative implications of physical sensations (anxiety sensitivity) was associated with activation in the medial PFC (i.e., the cognitive-evaluative aspect of pain), which has been linked with self-reflective processes [132].

In conclusion, enthorhinal areas may play a role in anxiety-induced hyperalgesia by increasing activity at pain affective (e.g., the perigenual cingulate) and pain intensity coding (e.g., the mid-insula) areas. Hyperactivity at other pain related sites such as anterior and posterior cingulate and OFC, which are involved in the emotional aspects of pain, is also present in subjects who fear pain and could reflect central sensitization at these sites. Findings of activity in the VTA, PAG and RVM during anxiety-induced hyperalgesia are consistent with animal studies. Future studies need to investigate the functional role of these sites during anxiety-induced hyperalgesia in humans.

3.3. Catastrophizing

Pain catastrophizing is another construct that taps into a negative pain schema [133]. It shares statistically significant variance with broader negative affect concepts such as anxiety and depression [134]. In fact, there is some debate as to whether catastrophizing is a separate construct beyond negative affectivity in general [133,135,136]. As a maladaptive coping strategy [137], pain catastrophizing is probably one of the strongest predictors of negative pain-related outcomes [138], and it is, for such reasons, included as a separate construct here. It can best be described as a cognitive interpretation of pain as extremely threatening [136,139]. The phenomenon is associated with hypersensitivity to noxious stimuli [137], heightened pain intensity, increased disability [134,140] and difficulty disengaging from pain [141], and it may mediate heightened vigilance to pain [142]. It probably augments pain through enhanced attention to painful stimuli and heightened emotional responses [143].

The mechanisms underlying the relationship between pain catastrophizing and pain are largely unknown. Sullivan et al. [134] suggested that the cognitive-affective processes of pain catastrophizing enhance the experience of pain by altering central thresholds of excitability which over time increases pain sensitivity. However, this mechanism has not been confirmed as studies of the nociceptive flexion reflex (a spinal reflex that subserves withdrawal from potentially noxious stimuli) in humans fail to find an association between pain catastrophizing and the nociceptive flexion reflex [144]. Instead, pain catastrophizing and alterations in supraspinal endogenous pain inhibitory and facilitatory processes may be associated [133]. Weissman-Fogel et al. [145] studied the relationship between pain catastrophizing and DNIC in humans. They found a negative association, suggesting that pain catastrophizing is associated with diminished endogenous inhibition of pain. Consistent with this, Seminowicz and Davis [146] examined the neural structures involved in the hyperalgesic effect of catastrophizing. fMRI was performed in healthy individuals at two pain intensity levels. During mild pain, they found activity in regions linked to the affective, attentional and motor aspects of pain, such as the insula, rostral ACC, PFC and premotor cortex, to be positively correlated with pain catastrophizing scores. During more intense pain, catastrophizing was negatively correlated with prefrontal areas involved in pain control, such as the dorsolateral PFC [147], suggesting that pain catastrophizers may have difficulty disengaging from intense pain through a lack of top-down control. Also activity in the amygdala, right temporal lobe, posterior parietal and lateral SI were negatively correlated with PCS scores during moderate pain.

Catastrophizing may play a considerable role in maintaining pain in chronic pain conditions [135]. Gracely et al. [143] used fMRI to examine the association between catastrophizing and brain responses in a group of non-depressed fibromyalgia patients, which were classified as high or low catastrophizers based on a median split of residual catastrophizing scores. Similar to the studies in healthy volunteers, they found enhanced neural activity to blunt pressure in brain areas believed to be involved in attention to pain (dorsal ACC, dorsolateral PFC), emotional aspects of pain (claustrum) and motor aspects of pain (premotor cortex) in pain catastrophizers. In addition, they found enhanced activity in areas involved in the anticipation of pain (medial frontal cortex and cerebellum), suggesting that pain catastrophizers with chronic pain develop preconceived expectations about pain.

These findings imply that catastrophizing is associated with activity in brain areas related to attention to pain (e.g., the dorsal ACC, PFC), emotion (e.g., claustrum) and motor (premotor cortex) activity and, at least during moderate pain, reduced top-down pain modulation (e.g., from dorsolateral PFC), but to fully determine the mechanisms by which catastrophizing influences pain, and to determine if it can be distinguished from the effects of attention and negative emotions on pain, more research is needed. Most studies have measured participants' natural levels of catastrophizing and looked at its relation to pain. Future studies might benefit from manipulating levels of pain catastrophizing to help clarify some of the causal mechanisms underlying the relationship between catastrophizing and pain.

3.4. Stress

During stressful or fearful situations, the experience of pain is less severe probably as a protective response that allows the individual to focus on more urgent matters [46]. Multiple mechanisms appear to mediate stress-induced analgesia (SIA) (see Butler and Finn [46] for an excellent review). The most well-established is the endogenous opioid system, but also non-opioid mechanisms such as GABA-ergic, glutamatergic, cannabinergic and monoaminergic systems have been implicated in SIA [46,148]. Behavioural and pharmacological studies in animals have shown that lesions of the RVM, PAG and amygdala lead to a weakened SIA response [148,149]; the amygdala being a region that is particularly activated by stress/fear [150]. Neurons from the amygdala project to brainstem sites such as the PAG and raphe nuclei which in turn project to the dorsal horn as determined through animal studies [46,151,152]. To the best of our knowledge, imaging studies of SIA in humans to confirm or disconfirm these findings are currently lacking.

The intensity, duration and type of stressor may determine the type of SIA as well as the degree of the subsequent analgesia. The sequential exposure of rats to a series of inescapable foot shocks, for instance, resulted in both an early naltrexone-insensitive and a late naltrexone-sensitive analgesia [153]. Naltrexone is an opioid receptor antagonist [154]. In a forced swim test, SIA increased with more extreme temperatures [155], and the degree of SIA differed with the frequency and pulse-width of electric foot shock [156]. Thus, imaging studies will need to distinguish between different types of SIA. This is particularly important as it is still unclear whether the extent of SIA is a linear correlation of the intensity of the inciting stimulus. In fact, under some experimental conditions, stress can induce hyperalgesia instead of analgesia (stress-induced hyperalgesia) [157]. This response may be associated with the former anxiety-induced hyperalgesia (Section 3.2). In the literature, they are often not well differentiated. Research is needed to address if disparities exist between these two phenomena. The mechanisms underlying stress-induced hyperalgesia are poorly understood. Like in SIA [158,159], serotonin has been shown to play a role [160,161]. The differing actions of serotonin probably depend on the type of receptor activated by the stressor. Serotonergic receptor types 5-HT2, 5-HT3 and 5-HT4 enhance neuronal activity whereas receptor types 5-HT1A and 5-HT1B suppress neuronal activity [162]. The location of the 5-HT receptor in the dorsal horn, i.e., on excitatory versus inhibitory interneurons or projection neurons, may further determine the resulting outcome [162]. Overactivation and desensitization of opioid receptors may also contribute to hyperalgesia during prolonged stress [163–166].

Neuroimaging studies of stress-induced hyperalgesia are scarce. What appears to be the only study found chronic stress (rated on the perceived stress questionnaire) to be correlated with activity in right posterior insula, right dorsal posterior cingulate cortex, right PAG and left thalamus during rectal balloon distension in healthy females [167]. The authors suggested that chronic stress may reduce the ability to cope with pain due to impaired pain inhibition. Greater anxiety developed in the participants with the highest levels of chronic stress, suggesting that chronic stress may produce more anxious individuals.

In summary, neuroimaging studies on the relation between stress and pain are lacking. The only study, which, to our knowledge, has addressed stress and pain, suggests that chronic stress alters pain control from the PAG resulting in a greater pain experience. It is important that future neuroimaging studies assess the link between stress and pain as stress, besides being a normal response to the threat of injury [46], has become a public health issue, and has been shown to play a crucial role in chronic pain conditions such as fibromyalgia and irritable bowel syndrome. For excellent reviews on the two conditions, see [168,169].

4. Modulation by cognitive factors

A number of cognitive factors are also known to modulate pain. Also here neuroimaging studies in humans are important as animal studies cannot adequately address the concepts under study. The research to date has mainly focussed on placebo analgesia, modulation by attention/distraction and hypnosis.

4.1. Anticipation/placebo

Placebo analgesia has been known for centuries. It describes the fact that a supposedly inactive treatment can provide a substantial pain relieving effect in some patients whereas the term nocebo is used to describe the reverse situation (i.e., that an inactive treatment can exacerbate pain). Positive expectations are thought to underlie placebo analgesia whereas negative expectations may explain the nocebo effect [170]. Since it is critical in modern biomedicine to understand how a given treatment works, it is also important to elucidate the mechanisms of placebo (and nocebo). Neuroimaging techniques have considerably advanced our understanding of some of the intriguing mechanisms of placebo analgesia, and the reader is referred to several excellent reviews for in-depth discussions [171–173]. Early behavioural studies showed that placebo analgesia could be blocked by the opioid receptor antagonist naloxone, which indicates that the endogenous opioid system is involved in the placebo mechanism [174]. In a PET study, Petrovic et al. [175] demonstrated related neural mechanisms between placebo and administration of a short-acting opioid remifentanil. Most significantly, the rostral part of the ACC was activated in both conditions, and there were significant correlations between PAG activity and rostral ACC. Subsequent studies using fMRI have identified a reduction within a more dorsal part of the ACC, insular cortex and thalamus (i.e., areas of the 'pain neuromatrix') that correlated with subject-based reports of pain relief in a placebo condition [176]. Other studies in humans have shown increased activation of the rostral/subgenual ACC and increased connectivity to the PAG and the amygdala [177]. It has been pointed out that differences in methodology, such as subject selection (responders, non-responders), practice effects and neuroimaging modality (spatial resolution), could explain these findings [170].

Zubieta and Stohler have in a series of elegant human studies described more details of the mechanisms underlying placebo analgesia; thus placebo-induced activation of a distributed and opioid-sensitive network includes the rostral ACC, OFC, dorsolateral PFC, anterior and posterior insula, nucleus accumbens, amygdala, thalamus, hypothalamus and PAG (for a review, see Zubieta and Stohler [170,172]). Activation of these brain regions was correlated with subject-based reports of pain relief, affective ratings and motivated behaviour [178]. With the use of the radiotracer (11C-raclopride), it was also demonstrated that dopamine D2/3 receptors in the nucleus accumbens play a significant role in placebo analgesia [179–181]. Activity in the nucleus accumbens similarly correlated with the extent of placebo analgesia as well as with dopamine and opioid responses to placebo in a recent monetary reward expectation paradigm, consistent with a role for the nucleus accumbens in producing placebo analgesia (see Zubieta and Stohler [170]).

Unlike placebo, the nocebo response appears to be mediated by CCK because CCK antagonists (CCK-1 and CCK-2) can prevent the nocebo development of pain and hyperalgesia in a dose-dependent manner (for a review, see Colloca and Benedetti [182]). As mentioned in Section 3.2, CCK also taps into the anxiety domain, but pharmacological studies on experimental pain suggest that CCK is specifically involved in nocebo-induced hyperalgesia and only indirectly in anxiety [183].

Neuroimaging studies have also examined the nocebo response [173,176,184,185]. Using fMRI, Porro et al. [184] found increased activity in contralateral SI both prior to and during painful stimulation of a foot. Expected pain intensities correlated positively with activity in areas of the 'pain matrix', such as the ACC, anterior insula and medial PFC, and were associated with reduced activity in anteroventral cingulate bilaterally. Brain activity during anticipation (that is, prior to the actual pain) was similar to that during pain, although slightly lower, suggesting top-down facilitation of pain during anticipation. Using fMRI in a random pain-no pain dispersion paradigm, Sawamoto et al. [185] likewise found patterns of activity in ACC and insula during anticipation of pain to mirror those of 'real' pain. Such brain activity appeared to be greater during the presence versus absence of negative expectations (i.e., nocebo effects) [186]. Kong et al. [186] looked at fMRI brain signals and the influence of nocebo on these in a pain plus nocebo (pain expectation) versus pain-no nocebo paradigm. They found increased activity during nocebo in bilateral dorsal ACC, insula, superior temporal gyrus, left frontal and parietal operculum, medial frontal gyrus, orbital PFC, superior parietal lobule, hippocampus, right claustrum/putamen, lateral prefrontal gyrus, and middle temporal gyrus. Hippocampus activity was specifically correlated with activity in areas of the 'pain matrix' (e.g., ACC, insula, left SI), suggesting an important role for the hippocampus in generating nocebo hyperalgesia. Neuroimaging studies of nocebo-related effects and negative expectations have thus shown increased activity in areas of the 'pain neuromatrix', in particular the ACC, PFC and insula, which may be mediated by the hippocampus. However, no studies have so far tested the administration of nocebo substances (inert substances comparable to placebo substances) on nociceptive processing in the brain.

In conclusion, several neuroimaging studies have demonstrated that 'belief' is a strong modulator of perceived pain, and that it is associated with functional changes in frontal-limbic brainstem networks of the 'pain neuromatrix' [172]. However, there is a need for a more standardised research approach to clarify discrepancies in the effects of placebo analgesia and to investigate the functional connectivity between the many brain sites active during placebo analgesia. More research is also needed to determine the brain sites involved in the production of nocebo hyperalgesia.

4.2. Attention/distraction

Attention and distraction are other powerful mechanisms by which the pain experience can be modulated, and they probably play an indirect role in many of the former mentioned pain control mechanisms (see Sections on depression (3.1), anxiety (3.2) and catastrophizing (3.3)). Anxiety and catastrophizing may, for instance, make individuals more prone to attend to 'worrying' phenomena such as pain. Directing attention to a painful stimulus can increase its perceived intensity and unpleasantness [187]. But the pain experience can also be reduced if a cognitive task is performed during the exposure of a painful stimulus [188]. Both A-δ and C-fiber input is subject to modulation by attentional mechanisms [189,190]. A series of studies showed attentional modulation of activity in pain-related brain regions, such as thalamus, SI, ACC and insular cortex [47,188,191–195]. Heightened SI activity during attention to a painful stimulus is a common finding in attention modulation studies [47,193,196–198]. Heightened aINS activity during attention to a painful stimulus has also previously been reported [47,196] as has an inverse correlation between midcingulate cortex (ACC) and pain intensity ratings during directed attention towards pain [47]. In the same study, ACC activity was also positively related to pain intensity during attention to auditory tones (i.e., during distraction from a painful stimulus), suggesting some non-specified role of the ACC in guiding attention [47].

Distraction studies show complementary findings. Frankenstein et al. [199] found a reduction in activity of the anterior cingulate gyrus (BA24) to cold pressor stimulation during a distraction task, and decreased activity in the right ACC and the right PFC was found when visceral pain was induced during distraction [195], consistent with reduced activity in pain-related brain areas. Similarly, an MEG study of distraction from second pain caused by CO_2 laser stimulation showed reductions in SI, SII-insula, cingulate cortex and medial temporal area [189]. In a PET study, Petrovic et al. [188] furthermore showed that distracting individuals with a cognitive task during cold pain, reduced activity in SI, SII and insula, areas involved in the sensory-discriminatory and affective dimension of pain. The reduction of experimental pain via distraction with a Stroop task was also associated with reduced activation of the insula, thalamus and mid-cingulate region while other areas such as the perigenual cingulate area and OFC showed increased activation, suggesting that these areas are involved in the modulatory effects related to attention [191]. It was also shown that distraction increases activity in the PAG [200]. This study thus suggests that top-down-modulation contributes to the pain reducing effects of distraction. Consistent with earlier studies, Valet et al. [201] showed that distraction is associated with reduced pain-evoked activity in SII, insula and thalamus, but with simultaneous increased activity in parts of cingulate cortex and OFC.

Studies on attention and distraction thus collectively suggest that attending to a painful stimulus increases activity in the 'pain neuromatrix' (e.g., in aINS, SI) whereas distraction reduces pain-related brain activity (e.g., in SI, SII, thalamus, insula, ACC). However, whether this occurs as a linear function of degree of attention/distraction is unclear. Distraction furthermore activates regions such as the OFC, perigenual cingulate and the PAG, suggesting that these are involved in the modulatory effects of attention. However, more research is needed to investigate the mechanisms underlying these effects. More research is, in particular, needed to clarify the mechanisms by which activity is heightened during directed attention towards pain. Many chronic pain patients become very occupied and focused on their pain making sustained distraction from pain difficult [202]. Some studies even suggest that chronic pain may worsen in response to distraction attempts [203,204].

4.3. Hypnosis

Hypnosis can not only shape the individual's perception and report of pain but also influence both the sensory and the affective components of pain. For example, hypnotic analgesia has been shown to reduce the unpleasantness and intensity of experimental pain in healthy individuals, and to be associated with different brain activation patterns in response to pain stimuli [205–207]. In clinical settings, hypnosis has also been shown to relieve pain (e.g., during and after surgical procedures [208,209] and in some chronic pain conditions [210–213]). In experimental pain studies with healthy participants, hypnotic analgesia has been shown to be associated with changes in pain thresholds and physiological pain correlates including brain activity [214–217], somatosensory event-related potentials (SERP) [218], and spinal reflexes [219,220]. Highly hypnotic susceptible individuals generally display larger reductions in perceived pain, reflex responses, and amplitudes of SERP to painful stimuli during hypnosis when compared to individuals with low hypnotic susceptibility [218,220].

Most of the imaging studies on hypnosis have been performed in highly hypnotic susceptible healthy individuals. Only a few studies have been conducted in chronic pain patients [221,222]. In an fMRI study of hypnotizable healthy volunteers, Schulz-Stübner et al. [223] compared activation of brain regions in response to painful heat stimulation with responses to the same stimulation during a pleasant hypnotic suggestion of a beach-wave-scenario. They found decreased pain and *increased* activation in anterior basal ganglia, left ACC and *less* activation in SI, middle cingulate gyrus, precuneus and visual cortex to painful stimuli during hypnosis than without. Using PET, Hofbauer et al. [205] investigated the effect of hypnotic suggestions for increased or decreased pain intensity following painful heat stimulation in healthy volunteers susceptible to hypnosis. Although increased activity of SI and SII was found during painful stimulation regardless of the type of hypnotic suggestion, such increases were greater in response to hypnotic suggestions for a pain increase than for suggestions of a pain decrease. Activation of the ACC was also detected, but this response did not differ between hypnotic suggestions for a pain increase or decrease, suggesting that the ACC may mediate both the facilitative and the inhibitory effects of hypnosis on pain. Another study using PET and EEG by Rainville et al. [206] examined the effect of hypnotic suggestions directed selectively at modulating (increasing or decreasing) the unpleasantness of painful heat stimulation in hypnotizable volunteers. They likewise found increased ACC and unaltered SI response compared with the alert condition independent of the type of suggestion. The studies by Faymonville et al. [214,215] also suggest the involvement of the ACC. They compared the effect of hypnotic suggestions (pleasant autobiographic memories) during painful heat stimulation with the effect of the same stimulus intensity without hypnosis in highly hypnotizable healthy people and found decreased pain and an increased ACC (mid-cingulate area) response in the hypnotic condition, suggesting the involvement of the ACC in decreasing pain during hypnosis. The authors [215] suggested that it is unlikely that the ACC modulated pain via attentional mechanisms as it is the more anterior areas of the ACC that are active in attention-demanding tasks (in contrast to the mid-cingulate area of the present study).

We have recently shown in chronic temporomandibular disorder (TMD) pain patients that, pain and unpleasantness scores during hypnotic hypoalgesia are significantly lower than in a 'neutral' control condition and significantly higher in a hypnotic hyperalgesia condition [224]. Using fMRI, we found painful stimulation in the control condition to be associated with activation of right posterior insula, SI, BA21, and BA6, and left BA40 and BA4 [224]. During hypnotic hyperalgesia, painful stimulation was associated with increased activity in right posterior insula and BA6 and left BA40 whereas hypnotic hypoalgesia was associated with activity in right posterior insula only. Somewhat unexpectedly, we found decreases in SI during hypnotic hyperalgesia compared to the control condition whereas decreases in right posterior insula and BA21, as well as left BA40 were found during hypnotic hypoalgesia compared to the control. These fMRI findings demonstrate that hypnotic hypoalgesia is associated with a pronounced suppression of cortical activity and a disconnection between patient-based scores and cortical activity in SI [224].

In conclusion, hypnotic suggestions of more painful (hyperalgesic) or less painful (hypoalgesic) conditions can strongly influence both the cortical responses of the 'pain neuromatrix' (e.g. SI, right posterior insula, ACC (mid-cingulate cortex), thalamus) and the behavioural aspects of chronic and acute pain, although results have not always been consistent. ACC activity was demonstrated both during negative and positive hypnotic suggestions, suggesting that the ACC mediates the influence of hypnosis on pain. Further studies will be needed to identify the specific neurotransmitters (e.g., opioids and dopamine) involved in these processes, but it may be expected – based on the available information and recent reviews – that hypnotic analgesia and placebo analgesia have some degree of overlap in terms of involved neurocircuitries [225].

5. Discussion

It is clear that the processing of nociceptive information is complex, and that the experience of pain can be modulated by a variety of mechanisms that either facilitate or inhibit nociceptive information. Somatosensory stimuli, such as noxious stimuli (DNIC), acupuncture and movement, can reduce the experience of pain and cortical activity in areas of the 'pain neuromatrix' whereas negative affect, such as depression, anxiety and pain catastrophizing, generally increase the experience of pain and increase activity in areas of the 'pain neuromatrix' (especially those related to the attentional and affective dimension of pain) as does chronic stress. However, extreme acute stress produces analgesia (SIA). The influence of positive affect on pain processing is less explored. Nonetheless, positive affect has been associated with more positive pain outcomes [95,98,226–228] and, for such reasons, should be investigated further. Also cognitive factors influence the experience of pain. Paying attention to a noxious stimulus enhances pain and increases activity within the 'pain neuromatrix' while distraction decreases its perceived intensity and associated cortical activity. Hypnotic suggestions or suggestions of effect (placebo) or side effects (nocebo) can influence the experience of pain and activity within the 'pain neuromatrix' in either direction depending on the suggested effects.

Findings from imaging studies in relation to the above mechanisms are often complex, reflecting activation or deactivation at numerous brain sites and sometimes contradictory results, which have led some researchers to suggest that there may be functional segregation of areas within specific brain sites (e.g., cognitive and affective areas within the ACC) [50,215]. The complexity reflects one notable difficulty with imaging studies—the determination of the function of brain sites. In order to infer something about a particular pattern of brain activation, it is essential that studies seek to isolate the factor under investigation by controlling for other potential influences on brain responses prior to assessing the specific factor's influence on (or relation to) nociception. At present the differential pattern of brain activation (or deactivation) between an experimental and control condition is assumed to reflect the activity related to a particular pain mechanism and its effects on other brain sites. However, we have to be cautious of such interpretations as they are highly sensitive to statistical thresholding and the control condition used. Furthermore, correlations are assumed to infer functional connectivity, but these may be the net outcome of very complex and widespread interactions in the brain and nervous system rather than a reflection of direct connectivity.

Unfortunately, the multiplicity of the pain experience complicates efforts to isolate specific factors. In any individual, multiple pain modulatory mechanisms may be active simultaneously in a dynamic manner. For instance, a person being asked to immerse his or her hand in ice water during deep pressure stimulation of the forehead may simultaneously experience DNIC, SIA, anxiety and anticipated pain. After a while the person may become familiar with the stimulation reducing the person's anxiety, or the person may start to worry about the pain becoming intolerable (catastrophic thinking). These factors all add to the pain modulatory cocktail. A number of, especially affective, modalities (e.g., anxiety, pain catastrophizing, chronic stress) are furthermore closely linked to one another, complicating distinctions between the underlying pain mechanisms further. Finally, the contribution of aspects not linked to pain per se, such as motor responses triggered by pain, may also interfere with the brain patterns of pain processing [229].

Despite this, neuroimaging techniques have helped determine supraspinal sites involved in a number of pain control mechanisms. The PAG is one area that has consistently been shown to be activated across the majority of pain mechanisms; it probably contributes to the pain inhibitory effects of acupuncture, stress, placebo, and distraction, and it may play an indirect role in DNIC. It may also facilitate pain during anxiety. Decreased activity in the PAG (perhaps an inhibition of PAG activity) also appears to contribute to the pain enhancing effects of depression and pain catastrophizing. Activity in the RVM (including the NRM), known to relay descending modulation from the PAG, was also observed both during acupuncture analgesia and anxiety-induced hyperalgesia. A note should be made here, that it can be very difficult to confidently identify small nuclei in the brainstem using fMRI, MEG and PET. Other brain areas (e.g., the ACC, PFC, OFC and nucleus accumbens) may also be involved in a number of mechanisms, but their exact role is less clear.

A final note, neuroimaging studies have almost exclusively focussed on brain activity. Neuroimaging should also be performed further down in the central nervous system. fMRI analyses carry the potential to determine neural activity outside the brain such as in the trigeminal nucleus caudalis of the spinotrigeminal pathway and in the dorsal horn of the spinal cord. This would additionally allow investigation of spinal gating in humans. A recent study successfully demonstrated reduced neural activity in the dorsal horn ipsilateral to noxious arm stimulation in a well-established placebo analgesia paradigm [230]. Determining the consequence of pain modulation regimes at the spinal cord and in the spinotrigeminal pathway using fMRI analyses may help create a more full and coherent picture of the pain pathway, both under normal and pathological conditions. Activity in the brainstem and dorsal horn could be coupled with activity in the brain to improve our understanding of the connection between these levels of the pathway (functional connectivity) and may help determine the function of brain sites. Such research is essential, not only to help map the pain modulatory pathways under normal conditions, but also to shed light on the mechanisms that contribute to failed pain control in chronic pain.

Role of funding source

None declared.

Conflict of interest

The authors have no conflict of interest.

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