Review

Neurocognitive aspects of pain perception

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The perception of pain is sensitive to various mental processes such as the feelings and beliefs that someone has about pain. It is therefore not exclusively driven by the noxious input. Attentional modulation involving the descending pain modulatory system has been examined extensively in neuroimaging studies. However, the investigation of neural mechanisms underlying more complex cognitive modulation is an emerging field in pain research. Recent findings indicate an engagement of the ventrolateral prefrontal cortex during more complex modulation, leading to a change or reappraisal of the emotional significance of pain. Taking placebo-induced analgesia as an example, we discuss the contribution of attention, expectation and reappraisal as three basic mechanisms that are important for the cognitive modulation of pain.

The impact of cognitive processes on the perception of pain

Pain is a highly subjective sensation with a complex and often non-linear relationship between nociceptive input and pain perception. A variety of cognitive processes have been shown to influence pain perception and bias nociceptive processing in the human brain. One clear example is how the pain experience depends upon the focus of attention: it is perceived as less intense when somebody is distracted from pain [1], yet increases when attention is focused on pain [2]. Among the cognitive variables influencing pain, the brain mechanisms underlying attentional control have probably been the most extensively studied [3–9].

However, attentional processes do not stand alone. They interact with mechanisms supporting the formation of expectations about pain and reappraisal of the experience or meaning of pain, these, in turn, are influenced by prior experience. For instance, patients whose pain is resistant to medication might feel helpless and, as a consequence, allocate more attention to pain than other patients. Moreover, previous experiences enable us to interpret signs that signal the appearance or disappearance of pain. Patients who respond well to analgesic treatment might, for instance, already disengage from pain when they know that medication is available. Here, the medication acts as a cue for pain relief. This knowledge is used in placebo analgesia, whereby pain relief is induced by the assumption that one has received a potent painkiller [10]. Similarly, however, the pain might allocate more attention if the medication was accidentally left at home. Based on the knowledge derived from previous pain experiences and stimuli associated with it, a schematic model of pain develops that enables us to make predictions about future pain events. Neural mechanisms underlying learning and expectations about pain and their resultant effect on pain perception have been investigated in numerous studies [11–13].

Psychological pain research, however, emphasizes that the schematic model of pain is further influenced by more complex cognitions, particularly by those related to the perceived threat of pain [14–16]. This type of cognition focuses on the subjective meaning that pain has for the individual. For example, pain might be perceived as more threatening if one believes that it signals a life-threatening pathological process that will have a long-lasting impact on their life. Like attentional and expectational processes, such cognitions can amplify and also attenuate pain. A heightened perceived threat value of pain is associated with a negative psychological adjustment as reflected, for instance, by catastrophic thinking and increased anxiety levels [16], consequently producing higher pain-intensity ratings [17]. Importantly, higher threat values have also been linked to maladaptive coping and higher pain intensity levels in chronic pain sufferers [14]. Conversely, a reappraisal of pain that makes pain less threatening leads to a decrease in pain ratings (e.g. Ref. [18]), an aspect that has only recently become a focus of neuroimaging studies on pain (see Box 1 for differentiation of attentional control and cognitive change).

In this review, we summarize recent findings on (i) the neural mechanisms underlying the attentional control of pain, (ii) the influence of expectations, and (iii) reappraisal and discuss the involvement of these processes in placebo-induced analgesia as a clinical example of cognitive pain modulation. Although this article focuses on cognitive aspects of pain modulation, it should be noted that processes described here are closely related to emotional factors [19] and their impact on pain experience, which are reviewed elsewhere [20].

Neural mechanisms of cognitive pain modulation

Attention

Attention modulates perception and cognition by allocating processing resources to relevant external and internal

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1364-6613/$ – see front matter doi:10.1016/j.tics.2008.05.005 Available online 5 July 2008

Box 1. Emotion regulation

The term 'emotion regulation' refers to the conscious or unconscious increase and decrease of emotions [63]. Most commonly, emotion regulation is studied by presenting emotionally relevant material (e.g. aversive pictures) to a subject who is instructed to use a certain regulation strategy (e.g. distraction from the negative content). To categorize regulation strategies, Ochsner and Gross [64] suggested that each strategy can be described by its relative reliance on (i) attentional control and (ii) cognitive change. Distraction from an unpleasant stimulus, for instance, is strongly driven by attentional processes and only involves little (if any) cognitive change. By contrast, the volitional re-interpretation of negative stimulus material (e.g. by emotional detachment) predominantly relies on cognitive change involving the reappraisal of the threat value of the stimulus. Findings from neuroimaging studies indicate that reappraisal crucially involves activation of (right) lateral prefrontal cortex areas [65,66]. These brain regions are thought to either inhibit limbic activity (e.g. in the amygdala) or generate alternative contents to replace emotions [64,66].

events. It thereby amplifies behavioral and physiological responses to relevant events and attenuates responses to irrelevant events [21]. The highly subjective and behaviorally relevant experience of pain is particularly susceptible to these attentional modulations. Psychophysical studies indicate that attention can modulate sensory and affective aspects of pain, possibly mediated by a modulation of the spatial integration of pain [2,22,23]. Research during the past decades has started to unravel the underlying neural substrates. Functional imaging studies showed that distraction from pain reduces pain-related activations in most brain areas that are related to sensory, cognitive and affective aspects of pain, including the primary and secondary somatosensory cortices (SI and SII), thalamus, insula and anterior cingulate cortex (ACC) [3–5,7,24,25]. The results of electrophysiological studies provided additional information that attention affects later responses more than earlier ones [26]. Furthermore, attention yields an increase in functional coupling between key brain regions involved in pain processing [9,27], implying that attentional modulation does not only result in altered local activation but also affects the functional integration of activation. These attentional modulations correlate nicely with the perceptual effects and correspond well to attentional modulations of sensory processing in other modalities [28].

A pivotal question for understanding attentional modulations of pain is where and how these effects are exerted. Numerous studies in other modalities compared different levels of attentional control and identified circuitries of higher-order frontal and parietal areas, which are presumed to mediate top-down attentional influences on sensory processing (for reviews, see Refs [21,28–30]). There is no reason to doubt that these brain areas are also involved in the attentional control of pain. However, direct evidence for this is lacking, presumably because of the inherent difficulty in grading attention to pain (Figure 1). Pain attracts attention *per se* and can rarely be ignored. Researchers have tried to circumvent this problem by applying paradigms in which subjects actively engage in distracting tasks and compared these distraction conditions to conditions in which subjects attended to pain. This contrast compares different foci of attention and unravels the expected attentional effects on pain proces-

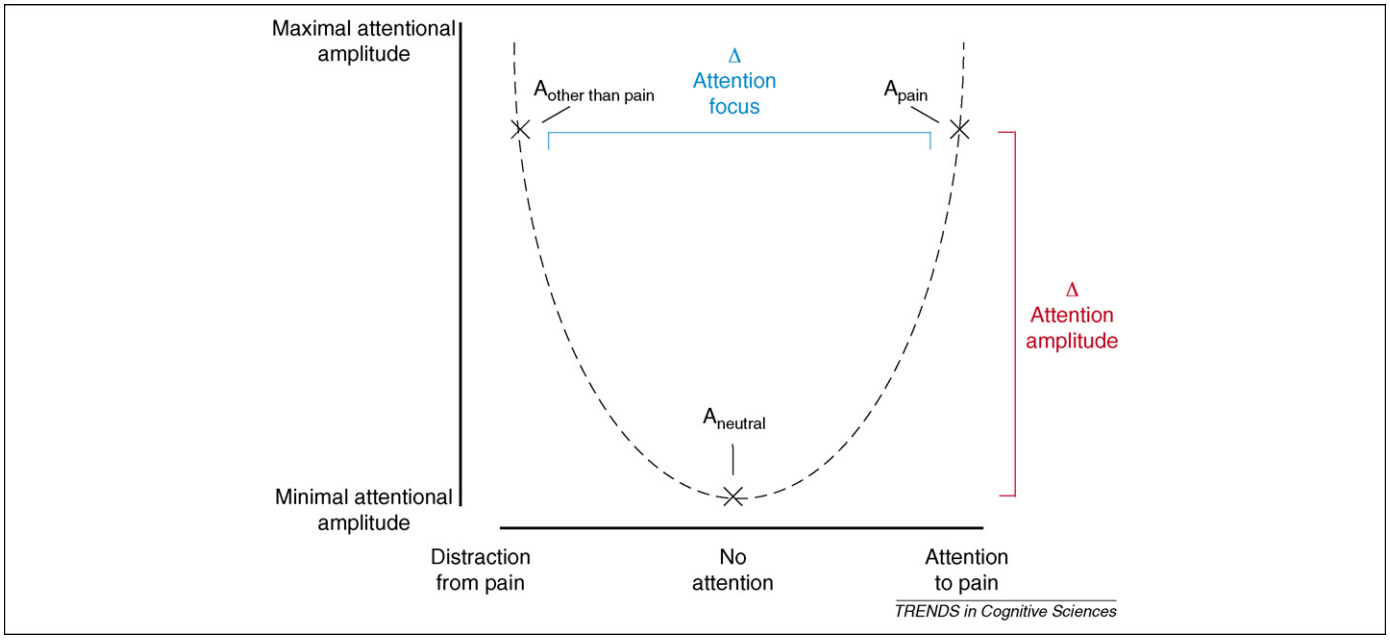

Figure 1. Investigating attentional modulation of pain. To investigate the effect of attention on pain, ideally, the perception and neural processing of a noxious stimulation when subjects focus all their attention on the stimulation (A_{pain}) would be compared with a condition whereby no attention is paid to the noxious input ($A_{neutral}$). The difference between the conditions provides an estimate for the influence that the amplitude or amount of attention has on pain (Δ attention amplitude). In most studies on attentional modulation of pain, subjects are instructed to either perform a discrimination task on the noxious stimulation or count the painful stimuli to keep the focus of attention on pain, whereas, typically no specific instruction is given in the control task. However, because pain automatically attracts attention (particularly in the absence of other sensory input), the validity of the 'no attention to pain' control condition is limited. Alternatively, attention to pain (A_{pain}) has been compared with a condition that is equally demanding of attention, but not focused on pain ($A_{other\ than\ pain}$). As an example, subjects were instructed to count deviant painful stimuli in the 'A_{pain}' (i.e. a short-lasting increase in temperature) and deviant acoustic stimuli in the '$A_{other\ than\ pain}$' condition [24]. Although this comparison (Δ attention focus) provides information about attentional processes specific for pain, it does not identify brain areas with activation level that co-vary with the amount of attention to pain. Note that the broken line represents a hypothetical inverted U-shaped relationship between amplitude and focus of attention.

sing. However, the level of attention might be similar for attention and distraction conditions (Figure 1), so the comparison of conditions does not enable identification of brain areas that specifically influence pain processing via attentional mechanisms. Moreover, even distraction paradigms cannot ensure that attention is effectively diverted from pain.

So far, attentional modulations of pain are supposed to share the general mechanisms and substrates of attentional modulations of sensory processing. However, the exceptionally close interaction between attention and pain seems to involve pain-specific features that are not necessarily known from other modalities. Interaction analyses taken during distraction from pain revealed brain areas that were more strongly activated than expected from the simple summation of distraction tasks and pain [4–6]. These areas particularly included the prefrontal cortex, ACC and the brainstem periaqueductal gray (PAG). Interestingly, these structures have been associated with descending pain modulation as characterized in animals [31] (Box 2). This network subserves opioid-mediated analgesia and mainly acts on the level of the spinal cord dorsal-horn. The results of the functional imaging studies indicate that distraction might at least partly act via activation of this descending pain modulatory system (see Ref. [32] for an overview). This is further corroborated by a study showing that distraction increases functional connectivity within this network [6] and the underlying descending cortical–brainstem pathways in humans are confirmed *in vivo* by diffusion tensor imaging [33]. Taken together, attention might modulate pain perception at least partially via a pain-specific opiate-sensitive descending modulatory pathway that regulates nociceptive processing largely at the level of the spinal cord dorsal-horn. This pain modulatory system might complement, interact and overlap with a more general system of attentional control, which has been well characterized in other modalities. Functionally, both networks might enable behavioral flexibility, which is limited by the involuntary attentional demands of pain.

Box 2. The descending pain modulatory system

Modulatory networks are likely to control nociceptive processing in the central nervous system. The descending pain modulatory system is probably not the only network, but is certainly the most extensively studied of these pain modulatory networks. It essentially comprises cortical, hypothalamic and brainstem structures, controls nociceptive dorsal horn neurons and is sensitive to opioids. Its description is originally based on the observation that, in rats, electrical stimulation of the brainstem can produce analgesia. Later work showed that these effects are at least partly mediated by modulation of nociceptive transmission in the spinal cord dorsal-horn and that similar modulations can be observed in humans. Current views of the descending pain modulatory system essentially include hypothalamus and brainstem structures such as the PAG and rostral ventromedial medulla, controlled by prefrontal, anterior cingulate and insular cortices. Main parts of the system are sensitive to opioids and it is thought to crucially contribute to opioid analgesia. However, descending pathways do not only inhibit but can also facilitate spinal transmission of nociceptive information, although these facilatory effects are less well studied. However, they might form the basis for how cognitive modulations amplify a pain experience (e.g. hypervigilance). Recent evidence shows that the descending pain modulatory system has a crucial role in a broad variety of adaptive and maladaptive modulations of the pain experience. (For a comprehensive review on the descending pain modulatory system, see Refs [31,32].)

Expectation

Expectations about upcoming events enable an organism to adjust sensory, cognitive and motor systems for adequate neural and behavioral responses. When a noxious stimulation is signaled by a cue, the expectation period between cue and stimulus is characterized by a signal increase either within or adjacent to brain areas that are subsequently activated by pain itself, that is, regions such as SI, ACC, insula, thalamus, PAG, cerebellum and putamen [34–37]. Crucially, the expectation of high pain intensity [37–39] and, consequently, increased anticipatory activation in contralateral SI, bilateral ACC, anterior insula and medial prefrontal cortex [35] were related to higher intensity ratings of subsequent pain.

During any perceptual process, expectations are compared to the bottom-up sensory information. These expectations are either confirmed or violated by the noxious input (Figure 2). Two recent functional magnetic resonance imaging (fMRI) studies examined the relative strength of expectations that bias perception when these expectations are violated [38,39]. To identify brain areas sensitive to the expectation of a decreased intensity, incorrectly signaled high-level pain stimuli were compared with correctly cued stimuli of the same stimulation intensity. Pain-intensity ratings showed that the same stimuli were rated as less intense when subjects were expecting a lower intensity. At the neural level, this expectation of a low- but application of a high-level stimulus was reflected by less activation in many brain areas related to pain processing compared with the matched 'high cue, high pain-intensity' condition. This finding indicates that the neural processing during stimulus application is crucially determined by prior knowledge of the stimulus. Interestingly, a bias towards increased pain (i.e. expectation of a high pain stimulus that is followed by low-level stimulation; Figure 2d) was neither observed in the pain-intensity rating nor at the neuronal level.

If expectations enable an organism to prepare for the upcoming sensory input, it is vital to detect discrepancies between expected and perceived features so that expectations can be updated if necessary. Ploghaus *et al.* [11] were the first to identify brain activation consistent with this violation of expectations. By using a model-based imaging approach they showed activation in the hippocampal system, superior frontal gyrus, posterior parietal cortex and cerebellum. The aim of this approach was to provide insights into 'how' the brain learns about pain over time by considering the history of successful (i.e. confirmed) and unsuccessful (i.e. violated) learning trials [40]. Subsequent studies used more complex algorithms to model learning about pain with a higher temporal resolution, enabling identification of brain regions involved in higher-order learning and the prediction of pain relief [12,13]. This promising computational approach will not only aid the elucidation of neural mechanisms underlying the influence of expectations on pain but also shed light on individual differences and biases in pain-related learning.

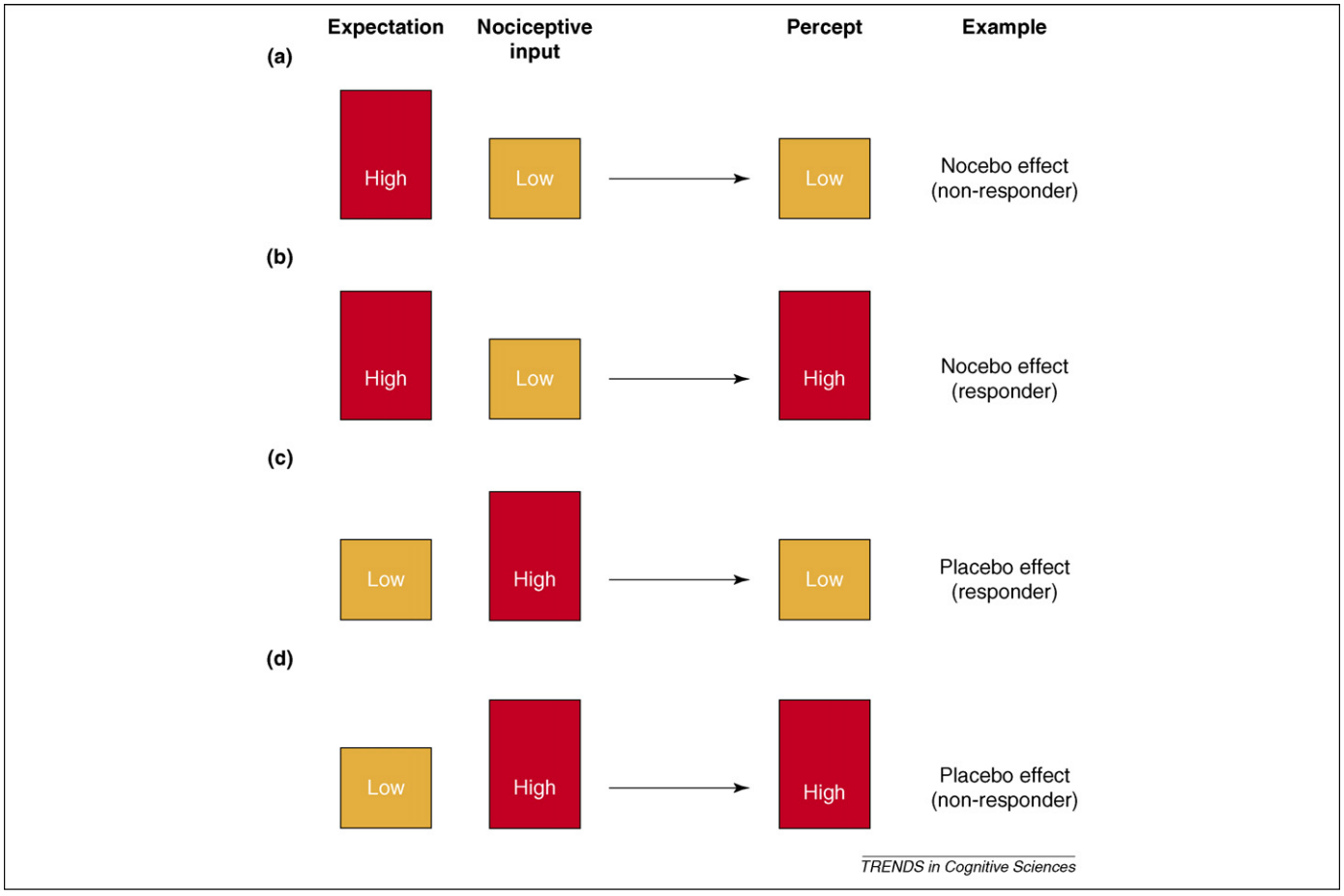

Figure 2. Violation of expectations and possible consequences. In an experimental setting, pain-intensity-related expectations can be induced by presenting the subject with cues that signal the intensity level of the next stimulus ('expectation'). In the example depicted here, we assume that only two stimulation intensities are applied: either a high-level (red) or a low-level (orange) thermal stimulus [38]. The subsequently applied stimulation ('nociceptive input') can violate the induced expectation in both directions: it can either be less intense – subjects cued to high-level pain but only received stimulation at a lower level than expected **(a,b)**; or more intense – subjects cued to low-level pain but received stimulation at a higher level than expected **(c,d)**. In both cases, the expectation can bias the perception so that subjectively rated stimulation intensity ('percept') follows the cued intensity level and is either rated as higher (b) or lower (c) than the actual nociceptive input. Alternatively, the nociceptive input can over-rule the induced expectation: a low-level stimulus is perceived as such despite a high-level cue (a) and, likewise, the high-level stimulus is appropriately rated although subjects expected a low-level stimulation (d). As an example, a positive placebo response follows scenario (c), whereas, in individuals who show no placebo-induced analgesia, the given nociceptive input has a stronger impact on the perception than the expectation (d). Likewise, the expectation of high-level pain (e.g. by the administration of an inert substance together with the suggestion that the pain might get worse as in the nocebo effect) might lead to an increase in perceived pain intensity (b) or not (a). (For an excellent review on nocebo hyperalgesia see Ref. [62]).

Reappraisal

Although pain is commonly perceived as threatening because of its warning character, the degree of threat depends upon the belief of the individuals in their own coping resources [41]. If coping resources are believed to be sufficient, pain can, at least to some extent, be perceived as controllable – a belief that has widespread positive repercussions: people who perceive a high degree of control try hard to initiate action and to persist in the face of failure. By contrast, people who perceive a low degree of control withdraw and show more passive coping in response to stressors such as pain (for an overview see Ref. [42]). Interestingly, the beneficial effects of perceived control are even observed if the controlling response is not used or only illusory, indicating that the underlying mechanism is a change in the meaning or reappraisal of an aversive event so that it becomes less threatening because control is possible [43]. Thus, perceived control is thought to trigger reappraisal processes that can change the pain experience.

Perceived control can be experimentally induced by allowing participants to stop a noxious stimulation. Self (or internal) control as opposed to external control over pain has been shown to reduce pain intensity [43]. Correspondingly, using fMRI, Salomons *et al.* [44] showed that perceived control over pain decreased pain-related responses in the ACC, insula and SII. Using a similar experimental set up, another study showed a possible prefrontal source of pain modulations related to perceived control [45]. Controllable versus uncontrollable pain was characterized by an increased activity in the right anterior part of the ventrolateral prefrontal cortex (VLPFC). The signal level in this brain region was negatively correlated with the subjective intensity of pain, indicating that it is directly involved in the down-regulation of pain. Moreover, in neuroimaging studies on emotion regulation, activation in the right VLPFC has consistently been observed when participants were instructed to use a reappraisal strategy to emotionally disengage from a threatening stimulus such as an impending noxious stimulation (Box 1). The right VLPFC might, therefore, have a pivotal role in the modulation of aversive stimuli based on reappraisal. Furthermore, activation of the right VLPFC before and during pain

has been shown to depend on the general belief of having control over one's own life [45] and the way the individual copes with pain [46]. The engagement of prefrontal brain areas in reappraisal is, therefore, not only driven by the current context but also crucially depends on personality traits. Nevertheless, locations of prefrontal activations in studies on reappraisal differed considerably. Whether and how these different locations within the VLPFC subserve different functions needs further investigation.

The placebo effect as an example of cognitive pain modulation

The placebo effect decreases pain intensity and cerebral responses to pain in brain areas such as the ACC, insula and thalamus [47–49]. It has recently been emphasized that it is obviously not the placebo substance itself that causes analgesia but the actual meaning we attribute to it [50]. Red placebo pills, for instance, are more likely to act as stimulants compared with blue placebo pills, simply because the color red usually has the meaning of 'up', 'hot' and 'danger'. Hence, the placebo induces particular expectations, depending on its appearance, prior learning and on the information about the effect it is supposed to have [51]. On a more abstract level, this might also involve reappraisal mechanisms along the lines of perceived control over pain, given that the placebo carries the information that it will effectively reduce the pain. The pain might, thus, be experienced as more controllable and less threatening. An involvement of reappraisal mechanisms in mediating the placebo effect is also indicated by neuroimaging studies that have consistently shown activation in the VLPFC [47,48] correlated with the reduction of pain during placebo [52]. These prefrontal activations have also been observed prior to the noxious stimulation [48], indicating an interplay between expectations and reappraisal in the placebo effect. It can therefore be speculated that the expectation of pain relief already engages mechanisms of cognitive change that lead to a reduction in perceived threat.

However, attentional control and the descending pain modulatory system are also likely to be involved in placebo analgesia. Benedetti *et al.* [10] suggested that appraisals of safety might promote self-distraction strategies, linking reappraisal processes with attentional control. Correspondingly, functional imaging studies showed placebo-related activations not only in areas related to reappraisal processes but also in areas related to attentional control and the descending pain modulatory system such as the dorsolateral prefrontal cortex (DLPFC), rostral ACC (rACC) and PAG [47,48,53,54]. Recent studies elucidated the interplay of these structures. Placebo-induced activations in rACC co-vary with neural activity in the PAG [47–49], indicating a direct modulation of the PAG by the rACC. Moreover, functional connectivity between the rACC and PAG, and also the amygdala, increased significantly during placebo analgesia [48,49]. A recent study using diffusion tensor imaging confirmed direct connections between rACC and PAG in humans [33]. Activation of the rACC most likely, therefore, recruits the opioid-dependent descending pain modulatory system to link the placebo effect with endogenous pain control [49]. By contrast, neural pathways engaging non-opioidergic control mechanisms that have consistently been shown in behavioral studies [51] are less clear. These results combined indicate that the placebo effect involves attention, expectation and reappraisal as basic mechanisms of cognitive pain modulation. On a neural level, this is reflected by recruitment of brain areas related to all these mechanisms and particularly by activation of the descending pain modulatory system. It is not yet established whether the descending pain modulatory system represents the final common pathway of all mechanisms that cognitively modulate pain to produce analgesia (descending inhibition) or increase pain (e.g. hyperalgesia and placebo) via descending facilitation. Clearly, additional direct cortico–cortical interactions are involved in both the placebo and nocebo effect in addition to other modulatory effects but they remain to be demonstrated.

Potential sources of modulation

Although brain areas such as the rACC or PAG show substantial activations during cognitive pain modulations, it seems unlikely that they are crucial for initiating pain modulation. PAG activity cannot explain further variance in a regression model on differences in perceived pain intensity after prefrontal activation has been considered [46]. Thus, the prefrontal cortex is more likely to represent a pivotal source of modulation. Anatomically, the prefrontal cortex is well suited to have this role: it receives sensory information from all modalities, and is associated with limbic structures that are crucial for affect and motivation such as the (para)hippocampus and amygdala. Furthermore, it has connections with motor system structures, enabling a direct translation of PFC outcome into behavior. Moreover, prefrontal regions are highly interconnected.

As discussed, activations in the DLPFC (comprising Brodman area 8, 9 and 46) have been found in studies on placebo-induced analgesia [47,55], particularly during the period before noxious stimulation [48]. In accordance with these findings, it has been hypothesized that the DLPFC is crucially involved in 'keeping pain out of mind' [56], particularly in chronic pain states (Box 3). This interpretation is supported by results from an analysis of the effective connectivity of this region with other brain areas, showing a modulatory influence on cortico–cortical and cortico–subcortical connections (i.e. thalamic–midbrain coupling). However, studies on placebo-related expectations [47,48] and perceived control over pain

Box 3. The prefrontal cortex in chronic pain

Prefrontal cortex activity is consistently seen in studies employing experimental models of chronic pain [67–71]. Most commonly, sensitization was associated with a signal increase in the DLPFC [68–71]. The functional significance of this activation is, however, still under debate: a positive correlation with the unpleasantness of pain indicates that DLPFC activation reflects altered cognitive-affective processing in the pathological pain state [56]. Additionally, increased DLPFC activations might reflect the recruitment of endogenous mechanisms of pain control. Correspondingly, patients with chronic pain show a decreased gray matter density in the DLPFC compared with healthy controls [72], indicating that its 'keeping pain out of mind' function [56] is substantially impaired in clinical conditions.

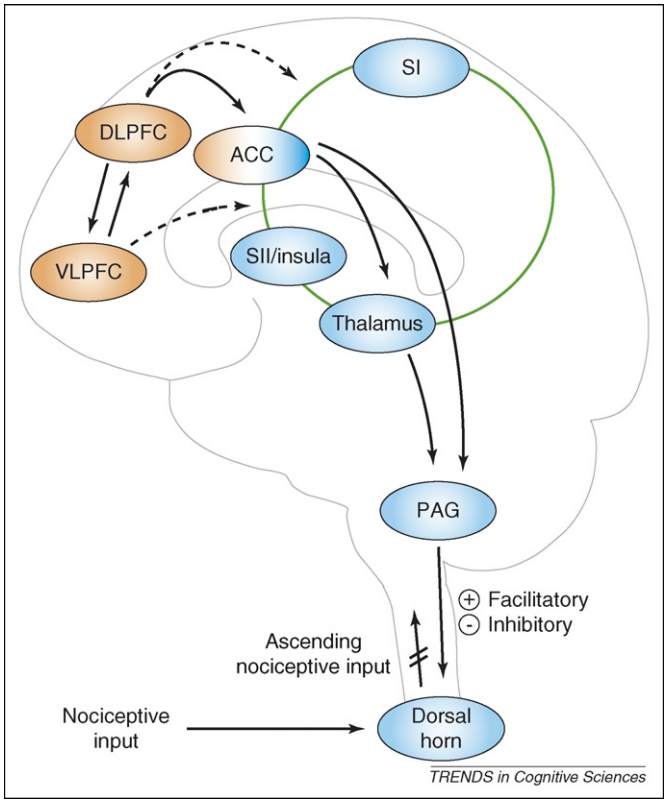

Figure 3. Possible neural pathways of cognitive pain modulation. Cognitive modulations of pain are related to activation of prefrontal brain areas (DLPFC, VLPFC and ACC; shown in orange), which modulate activation in pain-associated regions in the cortex (ACC, SI, SII/insula and thalamus), brainstem and dorsal horn (e.g. the PAG and dorsal horn; shown in blue). Attention has been shown to mainly engage the DLPFC and ACC, whereas reappraisal relates particularly to the VLPFC. Expectation has been associated with both densely interconnected prefrontal areas. The DLPFC is connected to the ACC, which, in turn, projects to thalamus and the PAG, a core component of the descending pain modulatory system. This system eventually facilitates and/or inhibits pain processing at the level of the spinal cord dorsal horn. Direct cortico–cortical modulations from VLPFC and DLPFC to pain-associated cortical areas are probable but have not been directly shown yet (broken lines). Areas most closely associated with pain (SI, ACC, SII/insula and thalamus) are densely interconnected, as indicated by the green circle. For the sake of clarity, ascending projections are not fully shown. Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PAG, periaqueductual gray; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; VLPFC, ventrolateral prefrontal cortex.

[45,46] provide evidence that the VLPFC is also involved in cognitive modulations of pain, reflecting reappraisal of the emotional significance of a stimulus resulting in a decrease in subjective pain intensity. It is still unclear whether this process is initiated by the VLPFC or the DLPFC, and as these two regions are highly interconnected, it implies a hierarchy might exist whereby one can influence the other to effect output (Figure 3). Further studies are needed to clarify how these prefrontal regions signal the needs, efforts and efficacy of cognitive modulations of pain.

Conclusions and future research directions

In this review, we propose that attention, expectation and reappraisal represent three key mechanisms of the cognitive modulation of pain and show how these processes contribute to placebo-induced analgesia as a clinical example of pain modulation. Figure 3 summarizes our current understanding of potentially specific and also common pathways for attention, expectation and reappraisal. It should be noted that this conceptual approach to differentiate these mechanisms does not at all preclude other mechanisms of cognitive pain modulations. However, other mechanisms are likely to imply one or more of these basic mechanisms between attention as a partially automatic, simple process and reappraisal as an effortful, more complex process. Further research is needed to characterize interactions between these mechanisms in real-life situations such as placebo-induced analgesia. Studies on catastrophizing (i.e. the tendency to focus on pain and negatively evaluate one's ability to deal with pain; see Ref. [57] for an overview), or stress-induced hyperalgesia and analgesia [58] might provide a profound basis for hypotheses-driven neuroimaging studies. Others, such as religion-based modulation of pain, have only recently become a focus of psychological pain research [59].

Studies on cognitive pain modulation could clearly benefit from neuroscientific work on related topics. Given that pain can be conceptualized as an emotion, studies on emotion regulation are probably closest to cognitive pain modulation (Box 1). However, there is also considerable conceptual overlap with research into anxiety and threat-biased sensory processing, with particular significance for cognitive modulation in chronic pain (for an overview see Ref. [60]). These studies indicate that heightened amygdala activity and reduced prefrontal recruitment bias an organism towards threat-related responses. At a cognitive level, this might reflect both increased activation of threat-related representations and a failure to activate alternative non-threat-related representations.

Although there is anecdotal evidence that cognitive processes can drastically modulate the perception of pain, the modulatory effect is generally much more limited and differs considerably between subjects. Placebo studies, for example, have taught us that the magnitude of the modulatory effect varies considerably between individuals. There is now a growing interest in the biological, psychological and social differences in responders and non-responders that will provide further insights into the mechanisms underlying pain modulation [51,61].

Future studies (Box 4) should use the wide range of psychological and neuroscientific tools and integrate already available knowledge from other domains of cognitive neuroscience such as cognitive control, learning, decision making or social interactions. These directions might provide a biological basis for a model on cognitive pain modulation, which can make predictions about interindividual differences in coping behavior and its

Box 4. Outstanding questions

- Which pain-related brain areas are particularly sensitive to top-down influences? Which are not and might, therefore, be driven mainly by peripheral input?
- At what level of neural pain processing do cognitive modulations take place?
- What is the differential role of the dorsolateral and the ventrolateral prefrontal cortices in pain modulation?
- How do different mechanisms of cognitive pain modulation interact in health and disease?
- What are the differential contributions of the descending pain modulatory system and direct cortico–cortical interactions in cognitive pain modulations?

manipulation by pharmacological and psychological interventions.

Acknowledgements

This work was supported by a Feodor Lynen Research Fellowship of the Alexander von Humboldt-Foundation (M.P.), the Templeton Foundation (K.W.), the Nuffield Trust (I.T.) and the Medical Research Council [Oxford Centre of Functional Magnetic Resonance Imaging of the Brain (FMRIB) Centre].

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