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Review

The influence of negative emotions on pain: Behavioral effects and neural mechanisms

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ABSTRACT

The idea that pain can lead to feelings of frustration, worry, anxiety and depression seems obvious, particularly if it is of a chronic nature. However, there is also evidence for the reverse causal relationship in which negative mood and emotion can lead to pain or exacerbate it. Here, we review findings from studies on the modulation of pain by experimentally induced mood changes and clinical mood disorders. We discuss possible neural mechanisms underlying this modulatory influence focusing on the periaqueductal grey (PAG), amygdala, anterior cingulate cortex (ACC) and anterior insula as key players in both, pain and affective processing.

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Introduction

The power emotions have over pain has been experienced by most of us in many facets. The headache that stops the minute the long-awaited visitor rings the door bell or the toothache that becomes unbearable after an argument with a colleague are well-known examples of this influence. For patients suffering from persistent pain this tight relationship between pain and emotions can have detrimental consequences. In their treatment of chronic pain, individuals with comorbid mental disorders feel more disabled and respond less favorably to rehabilitation than those with no co-occurring mental disorders (Dersh et al., 2002). Several population-based longitudinal studies have emerged supporting the hypothesis that mood disorders can increase the risk of developing chronic pain. Depressed, pain-free individuals for instance are on average two times more likely to develop chronic musculoskeletal pain than non-depressed, pain-free individuals (Magni et al., 1994; Carroll et al., 2004; Larson et al., 2004). Likewise, there is some evidence to suggest that anxiety disorders precede the onset of pain (Roy-Byrne et al., 2008). However, it should be noted that chronic pain in turn can lead to long lasting emotional disturbances often referred to as 'secondary pain affect' (Price, 2000). This might include worrying about the interference of pain with their life, difficulties of enduring pain over time and implications for the future. Often, this sets up a vicious circle where secondary pain affect aggravates pain which then fuels worrying and secondary pain affect. In a patient presenting with both, chronic pain and persistent mood changes, it is therefore often

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difficult – and maybe even clinically irrelevant – to determine the causal relationship between the two problems.

Current concepts of pain emphasize that the perception of pain is not necessarily linearly related to the noxious input, but is critically influenced by psychological variables. As a consequence of this assumed multidimensionality of pain, sensory aspects of pain (i.e., location, intensity and quality of pain) are differentiated and separately assessed from cognitive–affective aspects. That both dimensions can vary independently has been shown on a behavioral as well as on a neural level using hypnosis. Whereas hypnotic suggestions changing the sensory, but not the affective dimension lead to signal changes in the primary somatosensory cortex (Hofbauer et al., 2001), affective without sensory changes were correlated with activation in the anterior cingulate cortex (Rainville et al., 1997). In the light of such findings, it is not surprising that emotional factors commonly affect unpleasantness without necessarily changing the intensity of pain (Villemure and Bushnell, 2002, 2009; Villemure et al., 2003).

The differentiation of the two dimensions has turned out to be particularly useful in explaining pain-related disability. For instance, in a series of experiments on patients with chronic low back pain, Crombez et al. (1999) showed that pain-related fear is a better predictor of pain-related disability than pain intensity. Furthermore, the differentiation is important in understanding the pain-alleviating effect of interventions primarily targeting cognitive–affective pain aspects. Benzodiazepines, for instance, have been shown to provide pain relief, although they – at least in a strict sense – have no analgesic properties. It can be assumed that the pain-reducing effect of these substances is at least partly mediated by reducing anxiety and thereby the unpleasantness of pain (Dellemijn and Fields, 1994). A similar mechanism might underlie the beneficial effect of relaxation techniques which are commonly used in chronic pain (Molton et al., 2007).

In this review, we will summarize current evidence for a modulation of pain by negative emotions and discuss potential neural mechanisms underlying this influence. Before proceeding, it should be noted that in the literature on pain modulation, emotional factors are often differentiated from cognitive factors. The first comprise short-lasting moods (e.g., contextual anxiety, anger) as well as longer lasting emotional states such as clinical forms of anxiety or depression. In contrast, mental processes such as attention, expectation or catastrophizing are commonly referred to as cognitive modulators of pain. However, given their strong interdependance the two components are almost impossible to separate. In clinical depression, for instance, negative mood as the most prominent feature is almost inevitably accompanied by automatic thoughts, cognitive distortions, dysfunctional beliefs, and information processing biases (Beck, 2008). Likewise, cognitive processes certainly also have a strong emotional component. For example, if a substance is believed to increase pain (nocebo expectation) it seems reasonable to assume that this not only changes expectations, but also leads to anticipatory anxiety. It therefore has to be emphasized that a cognitive modulation of pain inevitably comprises an emotional response and that the influence emotions have on pain most likely include cognitive operations. However, in this review we will focus on studies explicitly addressing emotional aspects, discuss their outcome particularly in reference to the mature literature on normal and pathological emotion processing and only refer to cognitive processing where the direct interaction aids in understanding underlying mechanisms. For a recent review on cognitive modulation of pain see Wiech et al. (2008b).

Studies on the effect of mood induction on experimental pain

According to the motivational priming theory (Lang, 1995), the experience of emotions is determined by two opponent motive systems: the appetitive system that is activated by appetitive stimuli (e.g., sex, food) and results in positive emotions and the defensive system activated by harmful or potentially harmful stimuli (e.g., threat, pain) and resulting in negatively valenced emotion. If one of these motive system is activated (primed), future responses emanating from that system will be facilitated (Lang, 1995). For example, priming of the defensive system by negative emotion should facilitate the subsequent perception of pain. In accordance with this model, the majority of studies using mood induction on experimentally induced pain found that positive mood reduces pain perception (Zelman et al., 1991; Zillmann et al., 1996; Weisenberg et al., 1998; Meagher et al., 2001) whereas negative mood increases pain perception (Weisenberg et al., 1984; Cornwall and Donderi, 1988; Rhudy and Meagher, 2000; Wunsch et al., 2003; Kenntner-Mabiala and Pauli, 2005). Strategies to induce positive, negative or neutral mood comprise exposure to film scenes (Weisenberg et al., 1998; Zillmann et al., 1996), reading depressive, neutral or elative statements (Zelman et al., 1991), listening to various types of music (Tang et al., 2008), smelling pleasant and unpleasant odors (Villemure et al., 2003) and the presentation of emotive pictures (de Wied and Verbaten, 2001; Meagher et al., 2001).

Although the majority of experimental studies have pointed towards an increase of pain under negative emotions, there is also evidence for a pain-attenuating effect (al Absi and Rokke, 1991; Rhudy and Meagher, 2000, 2003). It has been argued that this apparently paradoxical finding might be explained by an interaction of emotions with the degree of threat or arousal they are associated with (Rhudy and Williams, 2005). In this view, high threat might elicit intense negative affect, high arousal, and reduced pain sensitivity — a phenomenon often referred to as stress-induced analgesia (Flor and Grusser, 1999; Martenson et al., 2009; for review see Ford and Finn, 2008 and Butler and Finn, 2009). In contrast, manipulations involving low threat might lead to low to moderately intense negative affect, low to moderate arousal, and heightened sensitivity to pain. Findings from a recent psychophysical study seem to confirm an interaction between emotion and arousal (Rhudy et al., 2008). Although the valence of stimuli presented for mood induction determined the direction of the modulation (i.e., increased pain during negative emotion and decreased pain during positive emotion) the magnitude of the modulation was determined by the level of arousal.

Experimental neuroimaging studies explicitly addressing the influence of emotions on pain are surprisingly sparse. Ploghaus et al. (2001) tested the effect of anticipatory anxiety on the perception and neural processing of pain. Painful heat stimuli were applied after either cueing for an uncertain temperature level (high anxiety) or a certain low level stimulus (low anxiety). Comparing low intensity stimulation under high to low anxiety revealed elevated pain intensity ratings when participants were unsure about the stimulation intensity. This modulatory effect of anxiety was reflected in an increased signal level in the enthorinal cortex of the hippocampal formation, a region that responds to aversive events whenever they form part of a behavioral conflict which biases the organism toward a behavior that is adaptive to the worst possible outcome and is accompanied by anxiety (Gray and McNaughton, 2000). Intriguingly, activation in the enthorinal region was closely related to signal increases in two pain-related brain regions, namely the perigenual cingulate cortex, associated with affective pain processing and the mid insula known to be involved in sensory processing. Two recent studies further confirm the relevance of this region in amplifying the pain experience in chronic pain patients with depression (Schweinhardt et al., 2008) and a functional pain disorder (Gundel et al., 2008).

Apart from this contextual influence of an emotion, it has been studied how trait-like individual differences in pain-related fear can impact on the neural processing of pain. Ochsner et al. (2006) found that the more subjects were generally afraid of pain (indexed by the Fear of Pain Questionnaire) the more they engaged the anterior and posterior cingulate and orbitofrontal cortex during painful compared to non-painful stimulation. All three brain regions have consistently

been implicated primarily in affective processing of pain, suggesting that a heightened fear of pain can up-regulate the sensitivity in regions encoding emotional aspects of pain. In contrast, anxiety sensitivity defined as the tendency to feel anxious about the negative implications of bodily sensations, had no direct impact on pain sensitive regions. It was, however, correlated with activity in the medial prefrontal cortex (MPFC) implicated in another study on anticipatory anxiety of pain (Kalisch et al., 2005).

Studies on pain in patients with clinical mood disorders

Experimental mood inductions offer the advantage of a defined onset of negative mood relative to pain, ensuring that changes in pain follow changes in mood. However, it can be argued that they have a very short-lasting effect and can therefore only be a first approximation to the investigation of long-term changes occurring in persistent mood changes. Studies investigating changes in pain sensitivity in populations with clinical mood disorders are therefore valuable additional sources of information. The high comorbidity between pain and mood disorders such as panic and post-traumatic stress disorders (PTSD; Gureje, 2008) or major depressive disorder (MDD; Bair et al., 2003) suggests an association with generally increased pain sensitivity. However, experimental data obtained in these clinical populations is surprisingly diverse. Although patients have reported lower pain intensity ratings than healthy controls for identical stimuli, relative hyposensitivity has also been found. This inconsistency might at least partially be explained by contextual factors and specificities within each of the different disorders researchers have only started now to explore in more detail. Patients with PTSD, for instance, have shown a heightened sensitivity to noxious stimuli (Asmundson et al., 2002), but can be associated with reduced pain sensitivity when patients are confronted with trauma-related stimuli (Pitman et al., 1990). Likewise, patients suffering from major depression can show normal or even reduced sensitivity to noxious stimuli applied to the skin (Bar et al., 2006, 2003, 2007; Dickens et al., 2003; Lautenbacher et al., 1994), but show hyperalgesia for deep somatic pain (Bar et al., 2005).

First insights into the neural mechanisms underlying altered pain processing in mood disorders come from recent neuroimaging studies in patients with major depression disorder. Bar et al. (2007) investigated brain responses to painful thermal stimuli in MDD patients and healthy controls. Only during a high pain condition did the clinical sample exhibit higher activation levels in left ventrolateral thalamus, the right ventrolateral prefrontal cortex (VLPFC) and the dorsolateral prefrontal cortex (DLPFC). Strigo et al. (2008) found that although the perceived pain intensity was comparable between unmedicated MDD patients and healthy controls, the clinical sample showed increased activation in the right amygdala and decreased activation in periaqueductal gray matter as well as the rostral anterior cingulate and prefrontal cortices during painful stimulation relative to non-painful stimulation. Furthermore, increased activation in the right amygdala during anticipation of pain was associated with greater levels of perceived helplessness. Using SPECT in patients with major depressive disorder, Graff-Guerrero et al. (2008) demonstrated that pressure pain compared to sham stimulation leads to increased activation in several brain regions including the amygdala and medial frontal gyrus that is abolished after antidepressant treatment.

Of particular interest are two studies which investigated the relationship between depressive symptoms and clinical pain. Giesecke et al. (2005) compared healthy controls to fibromyalgia (FM) patients with and without major depression and found lower pressure pain thresholds in both FM subgroups. However, only in the clinical sample with concomitant depressive symptoms did the painful stimulation induce bilateral amygdala activation and a signal increase in the anterior insula. The second study by Schweinhardt et al. (2008) focused on the augmentation of clinical pain in patients with rheumatoid arthritis (RA) in relation to the degree of concomitant depression. An activation cluster in the medial prefrontal cortex (MPFC) not only correlated with the degree of depressive symptoms, but seemed to mediate the relationship between depression and the relative number of tender joints as an indicator of clinical RA pain.

Data from recent behavioral studies suggest that the heightened pain sensitivity in hyperalgesia associated with depression or chronic pain syndromes accompanied by depressive symptoms such as fibromyalgia might be explained by a lack of descending inhibition or spinal hyperexcitability (Julien et al., 2005; Klauenberg et al., 2008). This is supported by a wealth of animal studies showing that sustained activation in facilitatory descending pathways may underlie some states of chronic pain (Gebhart, 2004; Porreca et al., 2002; Suzuki et al., 2004).

Evidence for reduced functioning of cortical regions involved in descending pain inhibition in fibromyalgia patients was recently reported by Jensen et al. (2009). Comparing individually calibrated painful to non-painful pressure stimulation, fibromyalgia patients showed reduced activation in the rostral anterior cingulate cortex relative to healthy controls, a region consistently found in pain modulation. Importantly, this reduced rACC activation was accompanied by a deficit in brainstem activation as previously shown in a study on neural correlates of placebo analgesia (Bingel et al., 2006).

Mechanisms underlying the modulation of pain by emotion

How can a feeling of sadness or anxiety lead to changes in the perception of pain? Most brain regions showing altered pain processing in the experimental and clinical studies mentioned above are part of the descending pain modulatory system. It comprises prefrontal, anterior cingulate and insular cortices, amygdala, hypothalamus and brainstem structures like the periaqueductal grey (PAG), rostral ventromedial medulla, dorsolateral pons/tegmentum, and the descending projections to the spinal dorsal horn (for an overview see Tracey and Mantyh, 2007). Although the descending pain modulatory system has predominantly been studied with respect to its pain-inhibitory effects, it has been shown that descending pathways can also facilitate spinal transmission of nociceptive information. Recent studies in animals have for instance identified a descending facilitatory projection from the periaqueductal grey (PAG) to the rostral ventral medulla (RVM), producing pro-nociceptive effects by enhancing spinal transmission of inputs from peripheral pain receptors (Carlson et al., 2007). In line with this finding, Rhudy et al. (2005) showed that unpleasant images enhanced the nociceptive flexion reflex, a measure of spinal nociception that is independent of supraspinal involvement.

In the following section we explore in more detail the basis of emotion-based 'tuning' of the PAG, amygdala, anterior cingulate cortex (ACC), anterior insula and prefrontal cortex. Given that these five regions are key players in both descending pain modulation and affective processing, they are well suited to link emotions with pain.

Periaqueductal grey (PAG)

The periaqueductal grey (PAG) is a brainstem nucleus that is closely connected to the rostral ventral medulla, thalamus, hypothalamus, amygdala and prefrontal cortex (Hadjipavlou et al., 2006). In addition to its anti-nociceptive properties, animal data suggest a substantial role in facilitating a heightened sensitivity to noxious stimuli (Gebhart, 2004; Porreca et al., 2002; Suzuki et al., 2004). In line with these findings, two neuroimaging studies by our group showed increased PAG activity with increased pain perception. The first study showed that punctate mechanical stimuli applied to experimentally sensitized skin lead to an increased PAG activation, as well the nucleus cuneiformis, compared to the application of same stimuli to healthy, untreated skin (Zambreanu et al., 2005). The

second study found a positive relationship between the level of anticipation and perceived intensity of pain which was reflected in the PAG signal level during pain, indicating that the more anxious the participants felt prior to pain, the more they activated the PAG and the higher the perceived pain intensity (Fairhurst et al., 2007a,b).

There is now cumulating evidence that such an emotion-related up-regulation of pain in the PAG is critically linked to the brain-gut peptide hormone cholecystokinin (CCK; Lovick, 2008). Interestingly, the effect that the CCK system has on pain appears critically dependent on a certain level of stress or arousal or anxiety. In rats exposed to a social conflict situation, enhanced responsiveness to nociceptor stimulation was seen in socially defeated (stressed) compared with non-defeated rats (Andre et al., 2005). This difference was abolished when the defeated rats were pretreated with a CCK_2 antagonist. Nociceptor stimulation evoked a strong increase in cortical CCK levels in the defeated (i.e., stressed) rats compared to non-defeated animals, which correlated with the significant increase in the levels of pain behavior exhibited by the former group. In humans, this CCKergic link between anxiety and pain has become apparent in anxiety-induced hyperalgesia or nocebo responses which can be reduced in the presence of CCK_2 antagonists (Benedetti et al., 2006, 2007).

An intriguing feature of CCK is the interaction with opioid-mediated systems which appears to take place at the level of the PAG. The injection of a CCK antagonist into the PAG potentiates opiate-mediated analgesia (Li and Han, 1989; Tortorici et al., 2003) whereas systematically administered morphine can be antagonised by micro-injection of a CCK agonist into the PAG (Li and Han, 1989). This is of particular interest in light of the opposing effects of placebos and nocebos. Given that placebo analgesia is mediated by endogenous opioids at least in some conditions (Amanzio and Benedetti, 1999; Zubieta et al., 2005), the findings on the involvement of CCK in nocebo hyperalgesia suggest that the opioidergic and the CCKergic systems may be activated by opposite expectations of analgesia and hyperalgesia, respectively.

Amygdala

The amygdala has long been known for its important role in emotion processing (for an overview see Phelps and LeDoux, 2005). Accordingly, an increasing body of evidence now strongly supports the concept of the amygdala as an important player in the emotional–affective dimension of pain (Gao et al., 2004; Ji et al., 2007; Neugebauer et al., 2004). Following the engagement by aversive stimuli such as pain, the amygdala affects a number of cognitive processes important for pain, namely the guidance of attention, conditioning as a form of learning, and memory retrieval (for an overview see Zald, 2003). To mediate an effect on attention, for instance, the amygdala uses two different pathways. First, the central nucleus sends projections to both cholinergic and noradrenergic cells capable of exerting widespread effects of attention (Kapp et al., 1992). Second, transitory feedback from the human amygdala to sensory cortical regions can facilitate attention and perception. This influence on cortical sensory plasticity may also result in enhanced perception for stimuli that have acquired emotional properties through learning. Fear conditioning which depends on amygdala plasticity alters the neural representation of an auditory conditioned stimulus in the auditory system. Stimuli that acquire behavioral importance gain increased representation in the cortex. For example, learning shifts the tuning of neurons in the primary auditory cortex (A1) to the frequency of a conditioned stimulus (CS), and the greater the level of CS importance, the larger the area of representational gain (Weinberger, 2007; Chavez et al., 2009). This suggest that emotional arousal can produce subtle shifts or biases in a primary sensory cortex area, a mechanism that allows the system to become more attuned to important events and to then attend to these more strongly in the future. So far, studies investigating such amygdala-driven baseline shifts in pain-related brain regions are lacking.

A region that is highly interconnected with the amygdala is the entorhinal cortex located at the rostral end of the temporal lobe. Besides its pivotal role in memory consolidation (Eichenbaum and Lipton, 2008), it has also been discussed in the context of emotion processing (Paz et al., 2006). In monkeys, lesioning of the entorhinal cortex is followed by enhanced defensive behavior not only to threatening, but also to non-threatening objects — a response that has been interpreted as an expression of systematic overestimation of risk (Meunier et al., 2006). In the context of pain, the entorhinal cortex has been found to exhibit a stronger response to anxiety-associated noxious stimuli compared to physically identical stimuli unrelated to pain without associated anticipatory anxiety (Ploghaus et al., 2001). Two more recent studies further confirm the relevance of this region in amplifying pain. Gundel et al. (2008) found increased activation in the entorhinal cortex in combination with the amygdala and anterior insula in patients with somatoform pain disorders. More specifically, we were recently able to show that enthorinal cortex activity prior to the onset of a noxious stimulation predicted the perception and neural processing of the subsequently administered stimulus (Fairhurst et al., 2007a,b) and in patients whose pain was augmented by depression these responses were functionally connected to activation in the medial prefrontal cortex (Schweinhardt et al., 2008).

Anterior cingulate cortex (ACC)

The anterior cingulate cortex (ACC) has been implicated in many functions related to emotion processing ranging from conflict resolution, and reward processing to the evaluation of socially relevant information (for review see Beckmann et al., 2009). In accordance with these suggested functions, malfunctioning of the ACC has been reported for post-traumatic stress disorder (Liberzon and Martis, 2006), major depressive disorder and bipolar disorder (Drevets et al., 2008) as well as anxiety disorders (Etkin and Wager, 2007).

In the pain literature the ACC is one of the most consistently activated structures (Apkarian et al., 2005). The dorsal ACC has mainly been implicated in the cognitive modulation of pain affect (Faymonville et al., 2000; Wager et al., 2004) whereas the signal level in the perigenual ACC has been shown to increase during placebo analgesia (Bingel et al., 2006; Petrovic et al., 2002; Zubieta et al., 2005).

In a recent meta-analysis on ACC structure and function, pain-related ACC activations showed extensive overlap with ACC activations in studies on emotions (although pain-related activations are usually found for posterior than emotion-related signal changes; (Beckmann et al., 2009) indicating that ACC activations found in neuroimaging studies on pain predominantly reflect affective pain processing). First evidence for this functional specification was obtained in a PET study where the sensory and the affective dimensions were modulated separately using hypnotic suggestions (Rainville et al., 1997). Changes in perceived unpleasantness but constant subjective intensity under hypnosis were accompanied by signal changes in the ACC. Since then, activation in the ACC associated with affective pain processing has been found in several neuroimaging studies on pain (Phillips et al., 2003; Tolle et al., 1999) and analgesic treatment (Sprenger et al., 2006). Furthermore, a recent fMRI study provided evidence that the ACC activation found during the modulation of pain is indeed related to emotions rather than attention (Villemure and Bushnell, 2009). In a direct comparison of both modulators, the attention effect was related to activation changes in the anterior insula whereas decreased pain unpleasantness following presentation of pleasant odors was reflected in signal changes in the anterior cingulate cortex, thalamus and somatosensory cortices.

Anterior insula

Like the PAG and amygdala, the insula is commonly found active in neuroimaging studies on pain (Apkarian et al., 2005) and has been associated with the descending pain modulatory system. Several lines of evidence suggest that the insula can be divided into a posterior division predominantly involved in sensory processing (Fairhurst et al., 2007a,b) and the anterior insula with connections to the limbic system (Craig, 2009).

In a recent fMRI study activation in the anterior insula was not simply driven by the noxious input but was more pronounced when participants were instructed to rate their subjective intensity of pain (Kong et al., 2008). This involvement of the anterior insula in the cognitive evaluation and subjective feeling of pain is in line with its proposed role in interoception, i.e. the monitoring of sensations that are important for the integrity of the internal body state and connecting to systems that are important for allocating attention, evaluating context, and planning actions (Craig, 2009).

In the emotion literature, a positive relationship between interoceptive awareness and the intensity of feelings (particularly of anxiety) has been postulated (e.g., Herbert et al., 2007; Pollatos et al., 2007). According to Salovey (2002), negative emotions such as anxiety can induce self-focus (or interoceptive awareness), and the attention directed to the self may enhance symptom detection and experience. In line with this theory, Gendolla et al. (2005) recently showed that negative and self-focus are necessary to foster the experience of somatic symptoms. The link between interoception and an increased feeling of anxiety might be provided by 'anxiety sensitivity' defined as a tendency of certain individuals to view interoceptive sensations as threatening (Reiss et al., 1986). Several lines of evidence indicate that the anterior insula cortex may be central for our understanding of anxiety sensitivity. Critchley et al. have suggested that the anterior insula processes visceral responses accessible to awareness as subjective feeling states (Critchley et al., 2004). Furthermore, it has been shown that the anticipation of unpleasant stimuli activates right insular cortex (Simmons et al., 2004), that anxiety-prone individuals have bilaterally increased insula activation during emotion processing (Stein et al., 2007), and that anterior insula activation can be attenuated by an anxiolytic drug (Paulus et al., 2005). Taken together, these observations strongly suggest that individuals prone to anxiety have heightened activity in the anterior insula during processing of certain kinds of salient stimuli. With respect to pain, it can therefore be assumed that the amplification of interoceptive processes by anxiety not only maintains anxiety but also pain as another "interoceptive feeling" (Craig, 2009).

But what information is encoded in this heightened activation in the anterior insula that leads to more pain? It has recently been proposed that the anterior insula not only receives interoceptive information but is also able to generate a predictive model (Paulus and Stein, 2006), which provides the individual with a signal of how the body will feel. Critically, individuals who are prone to anxiety show an altered interoceptive prediction signal, i.e., they experience an augmented signaling of the difference between the observed and expected body state. Findings from two recent studies support the notion that anterior insula generates an anticipatory signal of expected stimulus intensity that has an influence on subsequent perception. Lovero et al. (2009) showed that the anterior portion of the insula was notably active during anticipation of touch. Intriguingly, the degree of activation in the anticipation period was associated with ratings of perceived touch intensity and stimulus related processing in the sensory brain regions such as mid and posterior insula. Using high-resolution electroencephalography, Brown et al. (2008) were able to demonstrate that the anticipation of a pain stimulus depends on prior beliefs individuals have about the reliability of the cues predicting pain and that this influence is mediated by the anterior insula. As in the study by Lovero et al. (2009), there was a correlation of anticipatory activity in the anterior insula with the subsequent extent of pain modulation by anticipatory cues. This suggests a possible role for right anterior insula in mediating the influence of expectations on subsequent pain experience.

Emotional modulation of pain: the influence of prefrontal regions

Although structures such as PAG, amygdala and insula are certainly key players in implementing emotional modulation of pain, they themselves seem to be governed by prefrontal cortex regions (Mohr et al., 2008). Direct evidence for a crucial role of the prefrontal cortex in pain modulation comes from neuroimaging studies on emotional regulation and its effect on pain perception. If subjects are taught to emotionally distance themselves from the negative affective impact of pain, the resulting decrease in perceived pain intensity is accompanied by an activation of the right VLPFC (Kalisch et al., 2005). Intriguingly, the same brain region seems to be engaged when pain is felt as less intense during perceived control over pain (Salomons et al., 2007; Wiech et al., 2006) and engagement of religious beliefs (Wiech et al., 2008a). Based on these findings it can be hypothesized that a lack of lateral prefrontal cortex involvement provides the basis for the aggravation of pain and that this prefrontal hypo-responsivity is triggered by negative emotions. An impaired prefrontal functioning (in combination with an up-regulated amygdala responsivity) has recently been postulated to underlie pathological forms of anxiety (Bishop, 2007). More specifically, findings from studies in animals and humans suggest that an impaired prefrontal function contributes to alterations in learning about anxiety-related cues, selective attention to threat and interpretative biases often observed in anxious individuals. Intriguingly, individuals with a disposition to experience anxiety (high trait anxiety) show a reduced DLPFC during an attention demanding task when distracting information had to be ignored (Bishop, 2009), indicating impaired attention control.

It is typically assumed that the altered prefrontal cortex activity during emotional modulation of pain is necessarily accompanied by a complementary change in activation in pain-related brain regions (e.g. thalamus, primary somatosensory, anterior cingulate and insular cortices). Thus, an increased PFC signal level during reduction of pain should coincide with lowered activation in pain regions whereas higher pain levels should be reflected not only by a lack of PFC engagement but also higher signal levels in pain regions. Although this has been observed in a number of studies (e.g., Bingel et al., 2006; Salomons et al., 2004), there is also evidence that a modulation of pain sensitivity occurs without or with only a minor change in pain-related brain areas (Wiech et al., 2008a; Wiech et al., 2005). This raises the question whether emotional modulation necessarily has to involve a change in perception or whether it could also solely be based on appraisal processes following perception. So far, this issue has not explicitly been addressed with respect to pain. However, a recent neuroimaging study addressed a similar question regarding emotion regulation (Wager et al., 2008). Using a pathway-mapping analysis, Wager et al. found evidence for the assumption that activation of the prefrontal cortex leads to a reduction in negative emotion by impacting on structures directly involved in emotional experiences. A similar approach could aid in understanding the pathways and neural mechanisms underlying the emotional modulation of pain.

Future research directions

Despite the growing number of neuroimaging studies on emotional pain modulation there are still several open questions. First, studies using functional MRI to show changes in brain activity related to a change in perceived pain intensity are by nature correlative, not causal. Hence, data from these studies cannot prove a causal

relationship, for instance between increased prefrontal cortex activity and the effect emotions have on pain. Techniques such as transcranial magnetic stimulation (TMS; Bestmann, 2008) or transcranial direct current stimulation (tDCS; Been, 2007), however, can induce temporary functional lesions in circumscribed brain areas in the awake human. As such, these methods, therefore allow us to study their causal contribution to particular processes. The combination of these techniques with fMRI could reveal new insights into the functional significance of regions such as the prefrontal cortex.

Second, it is often assumed that the modulatory influence of cortical and subcortical structures is eventually put into action by changing spinal nociceptive transmission. However, there is evidence that cognitive–affective pain modulation can occur without altered spinal pain processing. For instance, Rhudy et al. (2006) investigated the effect of emotionally evocative pictures presented during application of predictable and unpredictable noxious stimuli on the subjective pain intensity and a spinal reflex (nociceptive flexion reflex, NFR) that does not require engagement of supraspinal structures. Intriguingly, they found that although the perceived intensity of both predictable and unpredictable pain was modulated by the affective pictures, changes in NFR magnitude were only seen during unpredictable pain. Future studies have to clarify which types of modulation require a change in spinal transmission and which are rather based on cortico–cortical or cortico–subcortical interactions. Third, previous studies have predominantly focused on the interaction between pain and anxiety and to a lesser extent on depression. However, psychological research suggests that other emotions such as anger, worry or frustration can also affect the perception of pain. Particularly the impact of anger has recently become a focus of attention that should be followed-up with neuroimaging techniques. Fourth, although it is now widely accepted that pain is critically determined by emotional processing, the experimental approaches and methods to measure the affective dimension of pain are often poor, particularly in neuroimaging studies. Either unpleasantness is not differentiated from pain intensity or – if it is – only crude scales (e.g., 4 point category of 5 point Likert scales) are employed. Furthermore, participants have to be instructed carefully as to how to use the scales and distinguish the pain dimensions. For an excellent example of the comprehensive assessment of the affective dimension of pain the reader is referred to Rainville et al. (2005) who conducted an elaborate set of experiments on emotional modulation of experimental pain (and autonomic responses). Without adequate psychometric methods neuroimaging studies might miss important brain regions or interactions between them.

Fifth, it has been pointed out that the quality of functional neuroimaging studies suffers considerably from “reverse inferences” (Poldrack, 2006), particularly if a topic under investigation is relatively new — such as the cognitive–affective modulation of pain. The term “reverse inferences” describes the logical error to conclude that the activation of a certain brain region (e.g., PAG) reflects a certain process (e.g., descending pain modulation) because this has been shown (or speculated) in previous studies, although their own experimental design has not tested for this particular function. Information on how to avoid reverse inferences and increase the interpretability of functional neuroimaging studies can be found elsewhere (e.g., Aue et al., 2009).

Sixth, it seems reasonable to assume that emotions not only have an impact on the perception of pain, but also on subsequent behavior such as decision making. Changes in decision making could therefore be an interesting (behavioral) read-out parameter in addition to subjective ratings of pain intensity and unpleasantness. Finally, the focus of previous neuroimaging studies on emotional pain modulation (and this review) has been on the impact of negative emotions. Their positive counterpart, represented as feelings of being safe (Wiech et al., 2008a; Wiech et al., 2006) or optimistic (Geers et al., 2008) are equally interesting and powerful and have recently been linked to reward processing in the context of placebo analgesia (Scott et al., 2007). A deeper understanding of their neural basis could not only broaden our view on pain, but also open new approaches to treatment of acute and chronic pain states (Leknes and Tracey, 2008).

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