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Topical review

Cognitive modulation of pain: how do attention and emotion influence pain processing?

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1. Introduction

There have been anecdotal accounts for centuries of people apparently experiencing little or no pain in situations that most of us would find excruciating. Yet, western medicine has given little credence to a patient's ability to modify pain. Instead, we focus on the pharmacological control of pain. For this reason, the vast majority of research on pain control has concentrated on peripheral and spinal cord mechanisms of opioid and anti-inflammatory analgesic therapy. Nevertheless, researchers are beginning to recognize that a variety of pain modulatory mechanisms exist in the nervous system, and these modulatory systems can be accessed either pharmacologically or through contextual and/or cognitive manipulation (Fields, 2000). Variables such as attentional state, emotional context, hypnotic suggestions, attitudes, expectations or anesthesia-induced changes in consciousness now have been shown to alter both pain perception and forebrain pain transmission in humans. These techniques, at times, preferentially alter sensory and/or affective aspects of pain perception, and the associated modulation of pain-evoked neural activity occurs in limbic and/or sensory brain regions, suggesting multiple endogenous pain-modulatory systems. This paper compares the modulatory influences of two principal cognitive variables, attention and emotion, on pain perception and addresses possible neural mechanisms underlying each of these influences.

2. Attentional modulation of pain

Probably the most-studied psychological variable that modifies the pain experience is attentional state. A number of reports show that pain is perceived as less intense when individuals are distracted from the pain (e.g. Bushnell et al., 1999; Levine et al., 1982; Miron et al., 1989; Rode et al., 2001). In many studies, distraction is achieved by requiring the subject to attend to another sensory modality, such as a visual, auditory or tactile stimulus (Bushnell et al., 1999; Longe et al., 2001; Miron et al., 1989; Rode et al., 2001), leading to a cross-modality sensory modulation similar to that observed in other modalities.

Other studies that have examined the effect of specifically focusing attention on pain have produced less clearly interpretable results. Levine et al. (1982) manipulated the attentional demand towards post-surgical pain by asking the patients to rate their pain more or less often. Those who rated it more often reported more pain, suggesting that focusing on pain enhances pain perception. However, other studies indicate that in certain individuals, focusing on pain may have the paradoxical effect of reducing its perceived intensity. For example, Keogh et al. (2000) observed that in an experimental situation males reported a lower cold-pressor pain sensation when they attended toward the pain than when they avoided it, whereas females did not show this effect. Similarly, Hadjistavropoulos et al. (2000) observed that chronic pain patients who were particularly health-anxious reported less anxiety and pain when they focused on the physical sensations. Thus, the effect of attention and/or distraction on pain may not be simple, but may be influenced by such variables as gender and personality type.

An additional complication in understanding the influence of attention on pain is the observation that pain itself modifies an individual's ability to focus attention. Pain is in general an attention-demanding modality, so that when a person is asked to divide his attention between pain and another sensory modality, attention to pain dominates (Miron et al., 1989). The effect of pain on attention may have particular importance in the clinical situation, since

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chronic pain patients show disrupted performance on attention tasks (Grisart and Plaghki, 1999).

The neural mechanisms underlying attentional modulation of pain are not fully known, but most likely involve various levels of the CNS. An opiate-sensitive descending pathway from the frontal cortex to the amygdala, periacquaductal gray matter (PAG), rostral ventral medulla and spinal cord dorsal horn has been studied most extensively and may be involved in attentional and/or emotional modulation of pain (Fields, 2000). The involvement of this descending system in attentional pain modulation is supported by a recent study in humans. Using functional magnetic resonance imaging (fMRI), Tracey et al. (2002) observed that activation in the PAG was significantly increased during a condition in which subjects were distracted from pain, and the level of PAG activity was predictive of the reductions in pain intensity produced by the distraction.

Nevertheless, other pathways and neurotransmitter systems could also be involved in cognitive pain modulation. The role of the cholinergic and adrenergic systems in attentional modulation of sensory transmission has been examined extensively in the visual system (Muir et al., 1992; Witte and Marrocco, 1997). Authors have proposed that these systems are involved in cognitive modulation of pain, but little experimental work has focused on their involvement.

Attention-related modulation of nociceptive neural activity has been observed throughout the afferent pain system. Neurophysiological data show that such modulation occurs even at the level of the dorsal horn, suggesting that descending modulatory control systems synapsing onto dorsal horn neurons may be invoked by changes in attention. Several studies have examined attention-related modulation of pain-evoked single-unit activity in behaving monkeys trained to perform tasks requiring attention to either a visual stimulus (distraction) or to a noxious heat stimulus in the receptive field of the neuron (attention to pain). Using this paradigm, investigators found distraction-related reduction of nociceptive activity in the medullary dorsal horn (Bushnell et al., 1984) and in the medial thalamus (Bushnell and Duncan, 1989), with less modulation in ventroposterior (somatosensory) thalamus (Bushnell et al., 1993; Morrow and Casey, 2000). These data suggest that attentional modulation of pain may preferentially involve pathways through the medial thalamus to the anterior cingulate cortex (ACC) – pathways shown to be involved in pain affect in humans (Rainville et al., 1997).

On the other hand, there is now evidence in humans and non-human primates that the responsiveness of neurons in primary somatosensory cortices (S1 and S2) to both non-painful and painful stimuli is altered by direction of attention. Neurophysiological studies in awake trained monkeys demonstrate that tactile neurons in S1 respond at a higher frequency to tactile stimuli when the monkey performs a task requiring attention to the stimuli (Poranen and Hyvärinen, 1982). Further, regional cerebral blood flow (rCBF) measured in human S1 cortex is higher when subjects attend to a tactile stimulus than when they attend elsewhere (Meyer et al., 1991). Thus, attentional state appears to modulate activity in primary somatosensory processing areas.

Psychophysical data show that attending to another sensory modality during pain results in parallel reductions in both perceived intensity and unpleasantness of the pain (Miron et al., 1989). Similarly, imaging studies show attention-related modulation of nociceptive responses in both sensory and limbic cortical areas, including S1, S2, ACC and insular cortices (Bushnell et al., 1999; Petrovic et al., 2000; Peyron et al., 1999). When subjects switch their attention between pain and another sensory modality, such as audition, parallel inverse effects are observed in somatosensory and auditory cortices. When the subjects attend to the pain, S1 activity is higher than when they attend to the auditory stimulus, whereas activity in auditory cortex is higher when subjects attend to the auditory stimulus than to the painful stimulus (Bushnell et al., 1999).

3. Modulation of pain by emotional factors

Psychological factors other than attention, such as mood and emotional state, also alter pain perception. Clinical studies show that emotional states and attitudes of patients have an effect on pain associated with chronic diseases (Haythornthwaite and Benrud-Larson, 2000; Schanberg et al., 2000). In the experimental context, manipulations that have a positive effect on mood or emotional state, such as pleasant music, pleasant pictures, and humorous films, generally reduce pain perception (Cogan et al., 1987; De Wied and Verbaten, 2001; Good, 1996; Meagher et al., 2001; Weisenberg et al., 1998; Zelman et al., 1991). Conversely, experimental manipulations that have a negative effect on mood and emotions have been shown to increase pain, although these effects are less reliable than those related to positive mood manipulations (De Wied and Verbaten, 2001; Meagher et al., 2001; Weisenberg et al., 1998; Zelman et al., 1991). Nevertheless, the interpretation of these studies is sometimes difficult, since they do not always clearly dissociate changes in mood from changes in attention. In fact, other studies show that emotional state can have a direct effect on attention to pain. For example, Keogh et al. (2001) found that subjects with fear of pain have an attentional bias toward pain-related information. Because of this attentional bias, testing pain after mood induction does not ensure the absence of covariate attentional processes.

A sensory modality that is highly linked to the limbic system and has unusually clear hedonic implications is olfaction. A number of studies suggest a particularly important role for olfactory stimulation in the alteration of cognition and mood (Alaoui-Ismaili et al., 1997; Marchand et al., 1999). Despite evidence indicating that mood and emotional states alter pain perception, few studies have examined the

effects of olfactory stimulation on pain. In rats, it has been found that exposure to positive odors decreases nociceptive reactions, whereas exposure to negative odors increases such reactions, especially when the intensity of nociceptive stimulation is low (Jahangeer et al., 1997). A preliminary report by Marchand et al. (1999) suggests that, in humans, odors influence both mood and pain in female subjects. Nevertheless, in both the animal and human studies of the effect of olfactory stimuli on pain perception, the influence of mood and attention has not been dissociated. Since most olfactory stimuli have clear positive or negative hedonic value and can also serve as a target for varying degrees of directed attention, the olfactory modality provides a useful tool for studying the interaction between direction of attention and emotional context on pain perception.

A study in our laboratory (Villemure et al., unpublished data) controlled and manipulated independently direction of attention and hedonic value of an odor distracter. We found that attention and odor valence independently altered pain perception. Further, whereas attentional manipulations had no effect on mood but altered the perception of both pain intensity and unpleasantness, odor valence altered both mood and pain unpleasantness but did not significantly affect pain sensation. These findings are consistent with those of Zelman et al. (1991), who found evidence suggesting that mood selectively alters the affective-reactive response to pain. When subjects' mood was improved by reading elative statements, pain tolerance (a measure of the affective dimension of pain) was increased, whereas when their mood was made worse by reading depressive statements, pain tolerance was reduced. Pain intensity ratings, which reflect the sensory aspect of pain, were unaffected by mood state.

To date, no study has directly addressed the neural mechanisms underlying the modulation of pain by emotional factors, including possible alterations in nociceptive processing in sensory and limbic cortical areas. Nevertheless, the observations that emotional manipulations alter pain unpleasantness more than pain sensation, while attention alters both pain sensation and unpleasantness, suggest that different modulatory circuits are involved. Further, because pain sensation is a primary contributor to pain unpleasantness and not vice versa (Price, 2000) and because the neural structures proposed to subserve the motivational-affective aspect of pain are accessed by other sensory modalities, such as taste and smell, emotional modulation of pain may well be subserved by cortico-cortical influences within the limbic system. Using hypnotic suggestions to alter pain unpleasantness without altering pain sensation, Rainville et al. (1997) found that pain-related activity in ACC is specifically modulated by changes in pain unpleasantness, suggesting that ACC might be an important site for hedonic modulation of pain. Another general cortical region that could be involved in hedonic modulation of pain is the prefrontal cortex, which is activated by stimuli with either positive or negative hedonic value, independent of stimulus modality (Royet et al., 2000). Imaging studies of pain show activation in this same area (Coghill et al., 1999).

As described in the previous section, it has been suggested that an opiate-sensitive descending pathway from the frontal cortex to the amygdala, PAG, rostral ventral medulla and spinal cord dorsal horn may be involved in emotional, as well as attentional, modulation of pain (Fields, 2000). However, there is evidence against such an involvement for at least some cases of emotional modulation of pain. In humans, systemic opiate administration alters both pain sensation and pain affect (Morin et al., 1999), whereas emotional state and mood at least sometimes alter only pain affect (Zelman et al., 1991). Nevertheless, although opiates modify both dimensions of pain perception, they appear to influence pain unpleasantness more than pain sensation (Morin et al., 1999), indicating that opiate receptors in limbic areas such as the ACC may contribute to the analgesia. Other evidence against the idea that the descending opiate-sensitive pathway to the spinal cord is involved in emotional modulation of pain is that the time-course of at least some emotional modulation does not fit with that of the descending opiate system, which has a slow onset and offset (Price and Barrell, 2000). Although some studies report late onset and/or an effect still present several minutes after the induction of the emotional state (Cogan et al., 1987; Weisenberg et al., 1998), others show a rapid onset and/or offset of emotional effects (De Wied and Verbaten, 2001). These temporal differences in emotional effects on pain suggest that different experimental paradigms may access different modulatory circuits. Most studies of emotional influences on pain do not control attentional state, so that attention could become a confounding variable invoking an additional modulatory circuit. Further, manipulations that produce extreme emotional changes involving stress or depression could produce a variety of physiological effects, including changes in catecholamine and/or endorphin levels (Resler and Nemeroff, 2000; Vaccarino and Kastin, 2000).

Several theories of emotions provide suggestions for neural systems that could underlie emotional modulation of pain. According to the *Motivational Priming Theory*, emotions are driven by two primary motive systems, appetitive (associated with positive affect) and aversive (associated with negative affect) which operate as opponent processes (Lang et al., 1992). Much of the work on this theory has been done using the auditory startle reflex, and it was found that negative affect (induced by pictures or odors) increases startle reflex while positive affect decreases startle reflex (Ehrlichman et al., 1997; Lang et al., 1992). In the case of aversive startle potentiation, the proposed neural circuitry includes the amygdala and PAG, both of which are components of the aversive circuit capable of modulating pain. A recent study showing activation of entorhinal cortex during the modulation of pain by anxiety (Ploghaus et al., 2001) at least indirectly implicates this circuitry in anxiety-related pain modulation, since there are strong reciprocal

connections between amygdala and entorhinal cortex (Pitkanen et al., 2000).

Neural circuitry that could subserve the influence of *positive* affect on pain processing is discussed by Ashby et al. (1999). These authors suggest that many of the behavioral influences of positive affect are mediated by the same neural mechanisms that mediate reward. They assume that for many of these effects, positive affect is associated with increased brain dopamine levels, notably in frontal cortical areas (i.e. prefrontal cortex and ACC). The concept that positive affect results in the release of dopamine and in turn influences cognitive functioning could well be extended to pain, since animal behavioral and neurophysiological studies provide considerable evidence for a role of forebrain dopaminergic systems in pain and analgesia (Lai et al., 1997; Magnusson and Fisher, 2000). Traditionally, these brain regions, which include the nucleus accumbens, the sublenticular extended amydgala of the basal forebrain, the amygdala, the ventral tegmentum and the orbital gyrus, have been thought to respond to rewarding stimuli, including pharmacological agents such as cocaine (Breiter et al., 1997). A PET imaging study found that intensely pleasurable emotional responses to music correlate with activity in brain regions implicated in reward, emotion or pain, including ventral striatum (possibly corresponding to the nucleus accumbens), dorsomedial midbrain (either PAG or pedunculopontine tegmental nucleus), amygdala, orbitofrontal cortex (BA 14), anterior cingulate cortex (BA 24/32), and insula (Blood and Zatorre, 2001). However, a recent pain imaging study brings support to the notion that there may be a shared neural system for evaluation of aversive and rewarding stimuli (Becerra et al., 2001). Using fMRI these authors demonstrated that noxious thermal stimuli produced not only the well-described activations in thalamus, S1, insula, ACC and prefrontal cortices, but also in the putative reward circuitry, including the sublenticular extended amygdala of the basal forebrain, ventral tegmentum/PAG, ventral striatum and nucleus accumbens. According to the authors, common activation of these regions for aversive and rewarding stimuli suggests that they may constitute a general circuitry which processes both rewarding and aversive information. Of particular interest, in one region of the nucleus accumbens, the direction of the signal change appeared to be opposite for aversive versus rewarding stimuli. This not only lends support to the view that pain and reward are at the opposite ends of the same behavioral spectrum but also introduces a means by which hedonically charged stimuli (either positive or negative) could quickly modulate pain perception.

4. Conclusions and future research directions

The available data indicate that attention and mood both alter pain perception. The mechanisms underlying these forms of cognitive pain modulation appear to be at least partially different, since they do not affect sensory and affective aspects of pain in the same manner. Future research should clearly focus on mechanisms underlying these different forms of cognitive pain modulation, including delineation of both neural circuits and neurotransmitter systems involved in the modulatory control of pain by cognitive state. Psychophysical, psychophysiological, pharmacological and brain imaging techniques could all provide important information. Nevertheless, the most fruitful studies will most certainly combine techniques, so that detailed perceptual information can be correlated with autonomic and brain-imaging measures, as well as pharmacological manipulations.

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