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Positive emotions and brain reward circuits in chronic pain

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Abstract

Chronic pain is an important public health problem that negatively impacts quality of life of affected individuals and exacts enormous socio-economic costs. Chronic pain is often accompanied by comorbid emotional disorders including anxiety, depression and possibly anhedonia. The neural circuits underlying the intersection of pain and pleasure are not well understood. We summarize recent human and animal investigations demonstrating that aversive aspects of pain are encoded in brain regions overlapping with areas processing reward and motivation. We highlight findings revealing anatomical and functional alterations of reward/motivation circuits in chronic pain. Finally, we review supporting evidence for the concept that pain relief is rewarding and activates brain reward/motivation circuits. Adaptations in brain reward circuits may be fundamental to the pathology of chronic pain. Knowledge of brain reward processing in the context of pain could lead to the development of new therapeutics for the treatment of emotional aspects of pain and comorbid conditions.

Keywords

Chronic pain; reward circuits; emotions; opioids; dopamine; motivation

Introduction

Chronic pain is an urgent medical problem world wide (Tsang et al., 2008). In the U.S., about 100 million people suffer from pain, costing approximately \$560–635 billion annually in terms of health care costs and lost productivity (Institute of Medicine Committee on Advancing Pain Research and Education, 2011). Patients with chronic pain often suffer from psychological and sociologic complications that are a further burden in addition to the already existing pain (Bair et al., 2008, Gureje, 2008). Chronic pain may develop from multiple causes including progressive disease conditions, such as diabetes resulting in painful diabetic neuropathy, or from injury or surgery. Surgeries such as inguinal hernia repair or caesarian section have been associated with an incidence of approximately 10% of

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patients progressing to chronic pain (Kehlet et al., 2006). However, the risk of chronic pain increases to nearly 50% with thoracotomies and amputations (Kehlet et al., 2006). As pain progresses from an acute origin, as from an injury or surgery, to a chronic condition, negative emotional states associated with chronic pain not only exacerbate physiological pain sensitivity (Borsook et al., 2013) but may also increase the incidence of comorbidities like depression, anxiety, anhedonia (e.g., the inability to experience pleasure), sleep disturbance, decision-making abnormalities, and even risk for suicide (Apkarian et al., 2004, Elman et al., 2013).

In spite of its prevalence and impact on patients' lives and on society, chronic pain and comorbid affective disorders are still poorly managed and current therapies are often inadequate (Backonja et al., 2006, Finnerup et al., 2010). Therefore, increased understanding of mechanisms that may underlie the affective aspects of chronic pain, and potential overlap with comorbid emotional states, are key factors in the development of new therapies. Pain is fundamentally aversive (Price and Harkins, 1992, Fields, 1999, Price, 2000). Pain aversiveness (unpleasantness) provides the physiological teaching signal to enable learning to avoid future harmful stimuli (Johansen and Fields, 2004) as well as motivation that underlies behavioral responses to escape from tissue damaging stimuli (Bushnell et al., 2013). Pain has been suggested to be a homeostatic emotion, resulting in autonomic responses and strong motivational demands similar to other aversive states such as hunger, itch, thirst, etc (Craig, 2003). Consistent with this concept, relief of pain, like relief of other aversive states, is rewarding (Craig, 2003, Denton et al., 2009). Studies in flies, rodents and humans demonstrate that cues associated with termination of an acute noxious stimulus will acquire a positive motivational valence and will support conditioned preference (reviewed by Gerber et al., 2014). Leknes and colleagues have investigated the interaction between pain, relief and reward in humans and concluded that pain relief is accompanied by pleasant sensations of relief at the end of a brief painful stimulation (Leknes et al., 2008). Emerging research provides new understanding of the brain circuits encoding emotional features of pain, and pain relief, and how these circuits may be altered in chronic pain states.

Pain processing in the brain

Sites activated by noxious stimulation and “signature” for pain

Recent advances in neuroimaging techniques and computational analyses have enabled investigators to noninvasively evaluate brain function in subjects, and in patients, increasing our understanding the circuits that could underlie the perception of pain. Neuroimaging studies have led to the identification of brain regions activated by acute noxious stimuli, including the primary somatosensory cortex (S1), secondary somatosensory cortex (S2), anterior cingulate cortex (ACC), prefrontal cortex (PFC), insular cortex (IC), amygdala, thalamus, cerebellum, periaqueductal grey area (PAG) and the mesolimbic reward circuit, which includes the ventral tegmental area (VTA) and nucleus accumbens (NAc) (Apkarian et al., 2005, Leknes and Tracey, 2008, Bushnell et al., 2013, Liang et al., 2013) (Figure 1). The somatosensory cortices (S1 and S2) and the insular cortex are believed to encode the sensory features of pain, which include quality (stinging, burning or aching), location and duration (Leknes and Tracey, 2008, Tracey, 2010, Bushnell et al., 2013). The prefrontal

region and the limbic system (ACC, PFC, amygdala, VTA and NAc) encode emotional and motivational responses, and are implicated in the affective and contextual aspect of pain (Leknes and Tracey, 2008, Tracey, 2010, Becker et al., 2012, Bushnell et al., 2013). The midbrain PAG is the primary control system for descending modulation of nociception as well as a host of other autonomic and emotional behaviors (Holstege, 2014). It is important to emphasize that these brain regions are not selectively or exclusively activated by nociception or restricted solely to pain perception; for example, the mesolimbic reward circuit is well known to be activated by natural rewards and rewarding drugs. Rather, regions serving several neurological functions including cognition, emotion, motivation and sensation are functionally connected in the context of nociception and together give rise to the experience of pain (Tracey, 2010, Tracey and Johns, 2010). The interactions among these sites also provide a means whereby emotional and motivational cues can alter the experience and perception of pain. Wager and colleagues have profiled the brain activation pattern for noxious heat perception in human volunteers (Wager et al., 2013)** identifying an apparent neurological “signature” of pain.

Alterations of brain function in chronic pain

Chronification of pain

While most pain conditions resolve over time, some will progress beyond the normal healing time into a chronic pain disorder (i.e., pain chronification). These chronic pain states are fundamentally different from acute pain in their underlying mechanisms, symptoms and in response to treatments. Neuroimaging studies have shown that chronic pain changes brain processing. Thus, chronic pain may be accompanied by alterations in brain structural features, functional connectivity or activity of these sites (Wood et al., 2007a, Baliki et al., 2010, Baliki et al., 2012, Hashmi et al., 2013). Importantly, many of these adaptations are observed in brain emotional and reward circuitries providing a possible explanation for high incidence of comorbid affective disorders in chronic pain patients. A recent longitudinal neuroimaging study followed subacute back pain (SBP) patients for one year and investigated whether brain changes could inform whether the patient would develop persistent back pain (SBPp) or would recover (SBPr) (Baliki et al., 2012)**. The authors showed that the adaptations in emotional and reward circuitries were predictive of pain chronification. Specifically, SBPp patients had greater functional connectivity between the medial PFC and the NAc than did SBPr patients at the first visit (i.e., before the chronification of pain), suggesting that this functional connectivity could be used to predict the chronification of low back pain (Baliki et al., 2012)**. Because the PFC is implicated in the processing of pain affect and the evaluation of the aversiveness of pain, this result implies that functional connection with the motivational/reward circuit could change the processing of pain perception. In a later study by the same investigators (Hashmi et al., 2013)*, the brain activation patterns in the early, acute/subacute and late back pain groups were compared with meta-analytic probabilistic maps related to the terms “pain”, “emotion”, and “reward” derived from neurosynth.org (Yarkoni et al., 2011). Brain activity in the early back pain group was limited to regions involved in acute “pain” (Figure 1), whereas after chronification of low back pain, the regions and activation patterns showed a greater overlap with those processing “emotion” including the amygdala and medial PFC (Hashmi et al.,

2013)*. It was concluded that chronic pain patients tend to process pain in emotion-related circuits to a greater extent than do those with subacute pain and recovery. Taken together, these studies suggest that increased connectivity between the reward circuit and the motivational-evaluation circuit may contribute to, and could predict, the chronification of pain. Anatomical and functional reorganization in reward/motivational and emotional circuits of chronic pain patients might explain emotional disorders often experienced by patients.

Disrupted reward circuit in chronic pain patients

The meso-cortico-limbic motivation/valuation circuitry comprising principally the VTA, NAc and PFC is critical to motivated and reward-seeking behaviors. Release of dopamine in the NAc from dopaminergic projections arising from the VTA is associated with behaviors indicative of reward expectation. Thus, the NAc plays a key role in motivating appetitive behaviors (i.e.; natural rewards such as drinking, eating and reproduction); these pathways may additionally be engaged by drugs that are intrinsically rewarding and that can lead to addiction (Wise, 2004). Recent studies suggest that the alterations or dysfunctions of the mesolimbic reward pathway contribute to the pathology of chronic pain (Farmer et al., 2012, Navratilova and Porreca, 2014). For example, in an imaging study, self-reported pain induced by hypertonic saline injection in healthy volunteers correlated with the amount of dopamine released in basal ganglia implicating dopamine activity in endogenous analgesia (Wood et al., 2007a, Wood et al., 2007b). In contrast to healthy subjects, patients with fibromyalgia did not show dopamine release in response to noxious stimulation (Wood et al., 2007a). Furthermore, activity of the VTA was decreased during both pain perception and expectation of pain relief in fibromyalgia patients (Loggia et al., 2013). Thus, while based on a small size of subjects, these findings suggest dysregulation of dopamine signaling in fibromyalgia patients. Dysfunction of reward circuitry has been described in other chronic pain syndromes such as burning mouth syndrome and atypical facial pain (see Jarcho et al., 2012 for review). Disruption of reward circuitry could therefore contribute to aberrant reward processing in chronic pain patients, however, further studies are needed to confirm this concept.

Possible mechanism that generates “pain relief” in the brain

Activation of the reward circuit

Several studies indicate that activation of the mesolimbic motivation/reward circuit contributes to both pain perception and pain relief. Consistent with the role of the mesolimbic circuit in reward learning and reward prediction, a neuroimaging study by Seymour and colleagues (Seymour et al., 2005) found that expectation of pain relief was associated with neural activity in the amygdala and midbrain. Furthermore, relief pleasantness produced by omission of pain was related to increased activity in the nucleus accumbens (Leknes et al., 2011). In a BOLD imaging study performed with healthy volunteers, the activity of NAc was decreased during onset of noxious thermal stimuli and was increased during offset of stimuli (i.e.; pain relief) (Becerra and Borsook, 2008)*. Similarly, in a subsequent study, NAc activations were observed in healthy volunteers during offset of noxious thermal stimuli (Baliki et al., 2010)*. In contrast, however, the

activity of NAc was decreased with the offset of the noxious stimuli in chronic pain patients (Baliki et al., 2010)*. Moreover, chronic pain patients rated the “unpleasantness” of the ongoing back pain as being reduced during the application of the acute noxious thermal stimuli suggesting that decreased NAc activity at the stimulus offset reflects aversion as the patient turns attention to his/her ongoing back pain. These results indicate a change in the valence of NAc response to termination of a nociceptive stimulus in the context of chronic, ongoing pain.

While human neuroimaging studies have shown that mesolimbic reward circuits are involved in pain relief, direct neurochemical evidence of the contribution of reward circuits on affective pain relief remain to be clarified. In contrast to clinical studies, it is difficult to evaluate the affective aspect of pain in experimental animals. Recently, various approaches have been employed in an effort to assess ongoing pain (Whiteside et al., 2013). Among them, the conditioned place preference (CPP) paradigm (Figure 2) enables the unmasking of the affective pain component in rats (King et al., 2009)*. Because ongoing pain provides a strong motivational drive to seek pain relief, motivational behavior in CPP paradigm can be utilized as an output measure of modulation of pain aversiveness in non-verbal animals (King et al., 2009)*. Treatments that are clinically effective against ongoing pain in humans were also effective in the CPP paradigm while treatments ineffective in humans are ineffective in CPP test (King et al., 2009, Navratilova et al., 2012, Navratilova et al., 2013). Studies using the CPP paradigm in rats are in agreement with the psychological investigations in humans that conceptualize relief of pain as a reward (Leknes et al., 2008, Navratilova et al., 2015a).

Whether relief of pain with treatments that are not intrinsically rewarding results in the activation of mesolimbic reward circuits was investigated in several experimental pain models. Navratilova and colleagues showed that CPP induced by the treatment for post-operative pain (peripheral nerve block by popliteal fossa lidocaine injection) is accompanied by activation of dopaminergic neurons in the ventral tegmental area and an increase in dopamine efflux in the NAc shell (Navratilova et al., 2012)**. In an animal model of migraine-related pain resulting from application of inflammatory mediators to the dura mater of rats, anti-migraine drugs induced CPP as well as increased dopamine release in the NAc shell (De Felice et al., 2013). These measures of rewarding effects of pain relief were abolished by pharmacological blockade of dopaminergic signaling in the NAc. Thus, human neuroimaging and preclinical *in vivo* studies suggest that relief of pain aversiveness is reflected in activation of dopaminergic neurons of the mesolimbic reward system.

Role of opioid circuits in the cingulate cortex for relief of pain aversiveness

In human imaging studies, activity in the anterior cingulate cortex (ACC) has consistently been reported following acute noxious stimulation (Apkarian et al., 2005) and the magnitude of the ACC activation correlates with subjective unpleasantness (Rainville et al., 1997). The ACC activity is also known to correlate with pain experience during emotional and cognitive tasks (Villemure and Bushnell, 2009, Bushnell et al., 2013) and during placebo-induced analgesia (Wager et al., 2004). Positron emission tomography (PET) imaging with opioid radiotracers suggest a major role for endogenous opioids in the ACC in reducing affective

aspects of pain (Zubieta et al., 2001, Wager et al., 2007, Zubieta and Stohler, 2009). Furthermore, opioid analgesics appear to act primarily within the ACC to modulate pain affect (LaGraize et al., 2006, Oertel et al., 2008). Other prefrontal cortical areas are additionally involved in the processing of chronic pain as well as relief from pain (reviewed in Becker et al., 2012, Denk et al., 2014).

The role of exogenous and endogenous opioids for relief of pain aversiveness was investigated in animal pain models. LaGraize et al., have shown that administration of morphine into the ACC of rats with neuropathic pain, selectively decreases the affective/motivational measures of pain resulting from repetitive evoked mechanical stimuli with no alteration of paw withdrawal threshold (LaGraize et al., 2006). We have additionally shown that ACC morphine treatment elicits release of dopamine in the NAc only in injured rats (Navratilova et al., 2015b). Furthermore, we have demonstrated that non-opioid pain relieving treatments require ACC opioid signaling to alleviate pain affect and activate reward circuits. Although opioid blockade in the ACC prevented CPP and dopamine release, it had no effect on behavioral thresholds to evoked stimuli. Similarly, systemic doses of morphine that had no effect on withdrawal thresholds, produced CPP and NAc dopamine release only in neuropathic, but not sham-operated rats. The anti-aversive effects of morphine were prevented by blockade of opioid receptors in the ACC. These findings provide a neural basis for the rewarding effects of pain relief that depend on opioidergic circuits in the ACC and downstream dopaminergic signaling in the NAc. Thus, endogenous opioidergic circuits within the ACC may be both necessary and sufficient for reward from pain relief (Navratilova et al., 2015b).

Conclusion

Neuroimaging is beginning to identify the brain circuits processing pain and emotions, as well as mechanisms that are likely to reflect pain chronification and affective disorders of chronic pain patients. Multiple studies have revealed that the regions relating to emotion learning and motivation play a crucial role for affective processing of pain and its relief. In addition, clinical and preclinical data suggested that relief of the affective component of acute and chronic pain is reflected by activation of reward circuits (Becerra and Borsook, 2008, Baliki et al., 2010, Navratilova et al., 2012). These insights can help to not only elucidate the pathology of chronic pain but may also be used as a way to develop new therapeutics for chronic pain. The development of new drugs for chronic pain is hampered by the lack of appropriate biomarkers. Recently, results of neuroimaging techniques suggested the possibility of biomarkers for pain (Borsook et al., 2011). For acute pain, Wager et al. showed that a specific brain activation pattern to thermal pain was attenuated by remifentanyl administration (Wager et al., 2013)**. Furthermore, Harris and colleagues indicated the aberrant alteration of brain function in fibromyalgia patients is resolved by a 2-week treatment with pregabalin (Harris et al., 2013)*. These results suggest that functional brain imaging could be a possible surrogate endpoint that could complement the visual analogue scale.

Although neuroimaging and *in vivo* research techniques in supraspinal circuit have enabled us to understand some important mechanism about pain and emotion processing, the precise

mechanisms that underlie pain chronification, and its relief, remain to be elucidated. Further effort is needed to develop new treatments targeting supraspinal circuits mediating chronic pain. The development of practical methods to measure pain, and its modulation, with neuroimaging will play an important role in advancing new mechanistic therapies.

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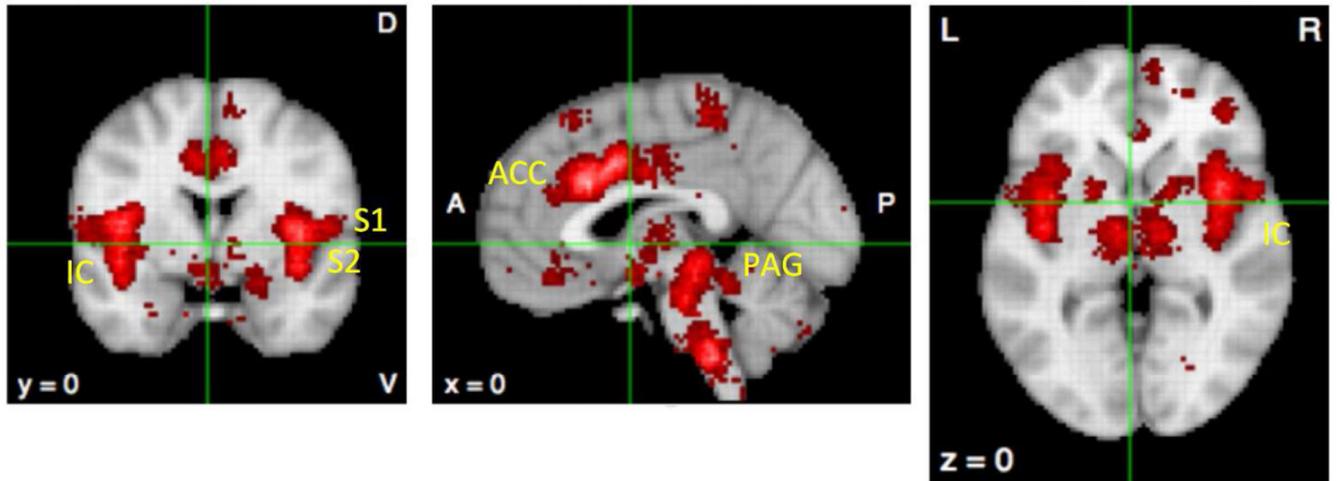


Figure 1. Neurosynth meta-analysis of 420 fMRI studies reporting the results on “pain”
The images show brain areas most commonly activated by pain stimulation including the primary and secondary somatosensory cortices (S1, S2), the insular cortex (IC), anterior cingulate cortex (ACC) and periaqueductal grey area (PAG). From: Neurosynth.org

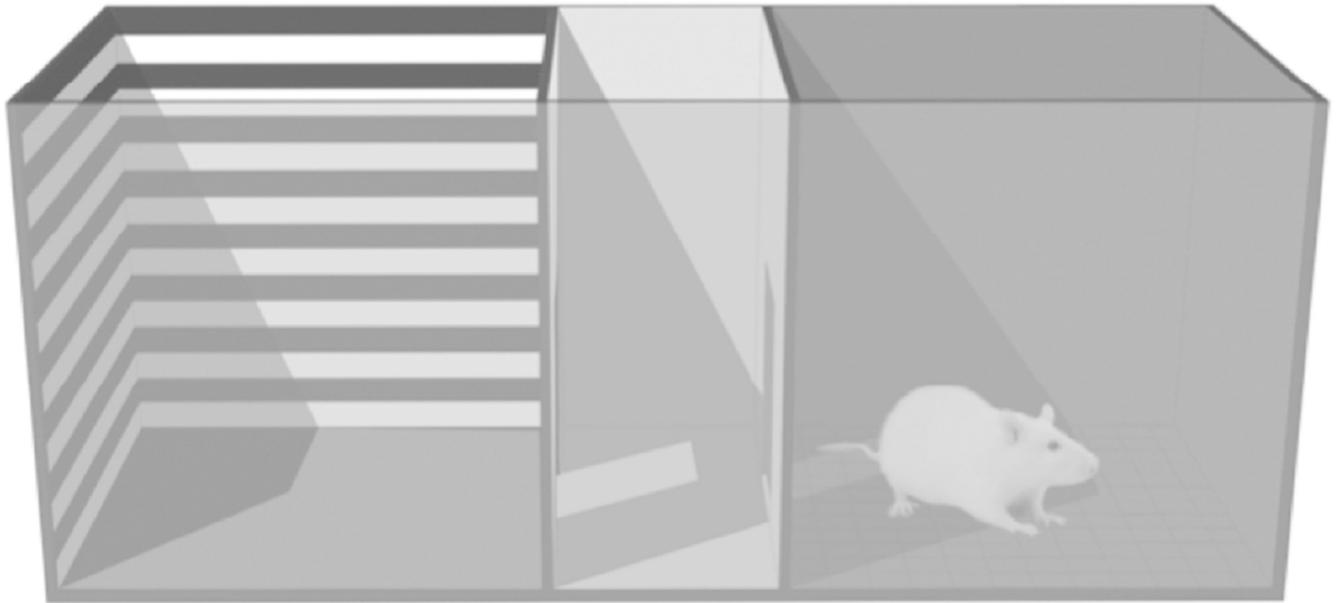


Figure 2. Conditioned place preference (CPP) paradigm

CPP can be used in rodents to reveal the presence of ongoing pain and the reward elicited by pain relief. CPP boxes usually consist of two conditioning chambers distinguished by different sensory cues that are connected by a middle (neutral) chamber. On pre-conditioning day, animals are placed into the CPP boxes with access to all chambers and the time spent in each chamber is recorded to ensure no pre-conditioning preference. During conditioning, animals will learn to associate one pairing chamber with vehicle treatment and the opposite chamber with pain relieving drug treatment. On test day, animals are placed drug-free in the CPP boxes with access to all chambers and time within each chamber is recorded. Increased time spent in the previously drug-paired chamber indicates preference for the pain relieving treatment.