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Top-down cortical control of acute and chronic pain

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Abstract

Acute pain has an evolutionary role for the detection of and response to physical harm. In some cases, however, acute pain can impair function and lead to other morbidities. Chronic pain, meanwhile, can present as a psychopathological condition that significantly interferes with daily living. Most basic and translational pain research has focused on the molecular and cellular mechanisms in the spinal and peripheral nervous systems. In contrast, the brain plays a key role in the affective manifestation and cognitive control of pain. In particular, several cortical regions, such as the somatosensory cortex, prefrontal cortex, insular, and anterior cingulate cortex, are well-known to be activated by acute pain signals, and neurons in these regions have been demonstrated to undergo changes in response to chronic pain. Furthermore, these cortical regions can project to a number of forebrain and limbic structures to exert powerful top-down control of not only sensory pain transmission but also affective pain expression, and such cortical regulatory mechanisms are particularly relevant in chronic pain states. Newer techniques have emerged that allow detailed studies of central pain circuits in animal models, as well as how such circuits are modified by the presence of chronic pain and other predisposing psychosomatic factors. These mechanistic approaches can complement imaging in human studies. At the therapeutic level, a number of pharmacological and non-pharmacological interventions have recently been shown to engage these top-down control systems to provide analgesia. In this review, we will discuss how pain signals reach important cortical regions, and how these regions in turn project to sub-cortical areas of the brain to exert profound modulation of the pain experience. In addition, we will discuss the clinical relevance of such top-down pain regulation mechanisms.

Keywords

pain; cortex; top-down regulation; limbic system; subcortical structure

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Competing interests

The authors declare that they have no competing interests.

INTRODUCTION

1. How pain signals reach important cortical regions

Pain plays a critical role in the interactions between psychological factors (e.g., depression and anxiety) and medical illness. This review provides background information about the neuroanatomical processes involved in both the bottom-up and the top-down processing of pain. The following topics will be addressed: (1) How pain signals reach important cortical regions; (2) The modulating role cortical projections to subcortical structures relevant to pain; (3) Implications for a neuromodulatory approach for pain treatment. The nociceptive system originates in the periphery. The primary afferent nociceptive neurons detect nociceptive signals, and then transmit these signals to the neurons of the dorsal horn of the spinal cord. These spinal neurons then project to the brain. Such “bottom-up” pathways are numerous and axons of the spinal neurons terminate widely in the brainstem, midbrain, and diencephalic regions such as the rostral ventromedial medulla (RVM), the parabrachial area (PB), the periaqueductal gray (PAG), the amygdala (AMY), the hypothalamus, and the thalamus. From here, neurons project to various cortical regions that are thought to mediate different aspects of pain [1]. The cortical areas most commonly acti-vated by a painful experience include the somatosensory cortices S1 and S2, the insula (IC), and the prefrontal cortex (PFC). These regions are part of a network of interconnected and interacting cortical structures that are triggered by a nociceptive input and in turn process and regulate the behavioral response to that input.

The sensory cortices S1 and S2 receive nociceptive signals from sensory nucleus of the thalamus, the ventro postero lateral (VPL) [2-4] and posterior triangular (PoT) thalamic [5]. Studies in both humans and animal models reveal that the nociceptive inputs into the S1 and S2 underlie, at least partially, the perception of sensory features of pain, including the location, timing and sensory qualities [3,6-10]. In a different pathway, the ventromedial posterior nucleus of the thalamus (VMPo) projects to the IC [5]. The strategic position of the IC enables interactions with several other cortical regions which makes it a well-investigated brain region for pain processing [11-13]. In addition, cortical pain processing involves the prefrontal cortex. In mammalian systems, the PFC can be divided in several main parts according to Brodmann (1909): the lateral prefrontal cortex (lPFC), the orbitofrontal cortex (OFC), and the medial prefrontal region including the anterior cingulate cortex (ACC) and the medial prefrontal cortex (mPFC).

The OFC is involved in many cognitive and sensory processes including response inhibition, value, prediction errors, rewarding and aversive aspect of sensory experiences including taste, odor, pleasant and painful touch [14]. Functional MRI (fMRI) studies indicate that painful touch produces greater activation of the orbitofrontal cortex than affectively neutral stimuli [15]. However, the exact role of OFC in pain states remains unclear. The role of the ACC, on the other hand, has been well established. Early cases of cingulectomy in humans already indicate its role in the aversive component of pain [16,17]. Electrophysiological recordings in animals [18-20] and human neuroimaging experiments further validated the importance of the ACC [21-24]. Both type of studies showed that the fundamental role of ACC lies in processing the emotional and aversive aspect of painful stimuli [25] as well as for

discriminating pain intensities [26-28]. Finally, animal studies have provided additional evidence for the involvement of mPFC in acute nociception. In rodents, neurons in ventral mPFC can respond to acute noxious stimuli [29,30]. Moreover, activation of the PFC output projection has been shown to inhibit pain [31-33].

The initial description of these aforementioned brain regions as part of a “pain matrix” has become more controversial recently, as studies in human brain imaging and animal models of pain have questioned the specificity of each of the regions in this network for pain processing [34,35]. For example, a recent report on human imaging highlights the complexity involved in defining the specificity of cortical nociceptive processing. In this study, in patients who suffer from a channelopathy that make them incapable of detecting nociceptive stimuli at the periphery, the application of a noxious mechanical stimulus continues to show activation of their ACC[36]. A simple explanation of these results is that the ACC does not necessarily process nociceptive information. However, an alternative explanation is that the activation of this pain matrix, or a nociceptive cortical and subcortical network, may represent multimodal or multi-sensory processing, including pain processing. In this model, Waxman and colleagues suggest that the magnitude of neural activation can be explained by the salience of the stimulus independent of input or sensory modality. Their model explains why imaging may show activation of the ACC in the absence of detectable nociceptive inputs at the periphery [37]. At the same time, studies have shown that the S1, S2 and insula cortices can be activated by nociceptive and tactile stimulation [22], and it is also possible that the activation of these neighboring cortical regions provide cortico-cortical activation of neurons in the ACC [38]. Nevertheless, the idea that select groups of neurons in select brain areas are specifically activated by a noxious signal and whose activation is sufficient and necessary to trigger a painful experience or behavior, has to be carefully interpreted. Likewise, the specificity of responses of this so-called pain matrix to nociceptive inputs has to be analyzed in greater detail in the chronic pain state as well.

In the chronic pain state, the S1, S2[39-43], as well as the insula[44,45] have been described to undergo changes in human imaging studies and studies of animal models. Animal studies further indicate that in the ACC, pyramidal neurons change their firing frequency [46,47], as intrinsic excitability in L5 pyramidal neurons is altered, and a loss of local bidirectional connections between pyramidal cells and fast-spiking inhibitory interneurons results in disinhibition[48]. Moreover, long-term presynaptic as well as postsynaptic changes occur in the ACC [49-51], which increase the probability of neurotransmitter release as well as the excitatory receptor response [52]. All of these modifications result in an increased output from the ACC in the chronic pain state. Finally, long-term changes of temporal precision of information coding in this region[53] also contribute to increased pain unpleasantness[28,54,55] and depression and/or anxiety[56]. These affective changes are thought to be mediated by the cingulate projection to limbic areas, including the amygdala. Meanwhile, in the mPFC, studies in human imaging as well as mechanistic inquiries in animal models suggest that structural[57-59] or synaptic loss can contribute to pain symptoms[60,61]. Such synaptic changes have been shown to be also involved in neuropathic pain in rodent models, via the recruitment of additional cortical areas[62].

Long term synaptic modification seems to be a common feature in these above cortical areas in the chronic pain state. With this in mind, one key hypothesis developed by Merskey and Bogduk (1994) is that "*chronic pain is a persistence of the memory of pain and/or the inability to extinguish the memory of pain evoked by an initial inciting injury*". According to this paradigm, peripheral injury and the resulting nociceptive inputs can trigger changes in the synaptic machinery in the cortex. When injury and pain persist for a long period of time, potentiation or stabilization of these synaptic changes occurs, which consequently generate abnormal firing of neurons in these pain-related cortical areas, in the presence of less intense peripheral sensory stimulation or no stimulation at all. Due to the strong connectivity between the cortex and limbic areas, altered activity in these cortical pain processing regions could therefore facilitate increased pain transmission to subcortical structures. This transition from acute to chronic pain state also represents a progression from a predominance of sensory pain circuitry to a predominance of affective pain circuitry in chronic pain states[63].

2. How does the cortex project to subcortical structures to modulate pain?

Numerous factors, including emotional state, attention, and memory of past painful experiences can engage multiple brain regions to profoundly modulate nociceptive inputs and give rise to a unique experience of pain. An understanding of these pathways that contribute to this top–down pain modulation can be useful for guiding the development of effective pain therapeutics.

2.1 Cortical modulation of the descending pain regulatory system—It is well established that nociceptive transmission in the dorsal horn of the spinal cord can be regulated by the descending pain regulation system involving the periaqueductal gray (PAG) and the rostromedial ventral medulla (RVM)[64,65]. This pathway has been described to be a hub for opioid mediated placebo hypoalgesia. The role of PAG was first described in the 1960s, when Reynolds and colleagues observed significant analgesia following electrical stimulations of the PAG in animals[66,67], and those results were later confirmed in human imaging studies[68]. Meanwhile, in animal studies, pain reduction generated by PAG stimulation can be attributed to the projections of neurons from the PAG to the rostroventral medulla (RVM) and the A7 noradrenergic nucleus of the medulla[69]. Neurons from the RVM are serotoninergic or GABA/glycinergic and can either activate or inhibit the spinal neurons[70]. Thus, a balance between these two descending (faciliatory and inhibitory) projections is critical for pain modulation. In the case of chronic pain, for example, this balance is shifted towards more pain facilitation than inhibition[71-73]. Therefore, this PAG-RVM pathway is a key analgesic target for opioids, cannabinoids and serotonin/norepinephrine reuptake blockers. This pathway is also an important target for cortical modulation.

The ACC has been shown to project both directly and indirectly, via subcortical regions such as the amygdala and the hippocampus, to the PAG[74]. Activation of the ACC via electrical or glutamatergic stimulation increases paw withdraw in animal studies, suggesting descending facilitation via RVM [75,76]. On the other hand, ACC activation has also been described to diminish neuronal responses to mechanical stimuli in a subset of spinal dorsal horn

neurons[76], probably due to the direct projections from ACC to the dorsal horn of the spinal cord[77]. These apparent opposite results suggest a high level of complexity in this descending modulatory circuit that warrants further investigations. Newer molecular tools will allow us to decipher the impact of the ACC on spinal pain circuits in greater details[78]. Moreover, other cortical regions can engage the descending pain regulating system. Robust mPFC-PAG projections have been confirmed in rodent pain models[79]. Furthermore, human imaging studies indicate that chronic pain disrupts this pathways in patients[80]. Finally, the insular cortex also modulates spinal pain transmission, as the injection of μ-opioid receptor agonists such as morphine produced an analgesic effect by decreasing the firing of spinal nociceptive neurons[81]. Increased GABAergic transmission and resulting inhibition of insular outputs provides descending inhibition of spinal nociceptive neurons[82], likely through an insular-PAG-RVM projection[83].

2.2 Examples of corticolimbic regulation of pain—While the PAG-RVM pathway is the most studied conduit for descending pain modulation, there are other subcortical targets for the cortex to exert top-down control of pain, such as the limbic system, including the amygdala and nucleus accumbens (NAc). Interestingly, various regions of the insular cortex, PFC and ACC have been shown to project to these limbic regions. Unfortunately, the mechanisms of corticolimbic regulation of pain are less well-characterized.

2.2.1 Prefrontal cortex – amygdala projection in acute and chronic pain regulation: The amygdala plays a central role in the affective aspect of pain. Indeed, this group of sub-cortical nuclei is well known in the control of fear and related emotions[84]. Overall, the amygdala is considered to provide an emotional value – either positive or negative – to sensory information, particularly involved in aversive or fear – memory. The central nucleus of the amygdala (CeA) receives nociceptive inputs from the dorsal horn via the parabrachial area (PB)[85-87]. The lateral-basolateral amygdala (LA-BLA) receives sensory and affect-related information from the thalamus and the cortex [88]. CeA processes can be influenced by direct glutamatergic projections from the BLA and by indirect disynaptic routes involving inhibitory GABAergic neurons in the intercalated cells (ITCs)[89,90]. CeA is the output nucleus of the amygdala that modulates pain behavior through projections to descending pain control centers as the PAG[88,91].

The bidirectional projections between the amygdala and the prefrontal are well-studied in animal pain models. Under chronic pain conditions, synapses between the BLA and the CeA are potentiated, resulting in increased excitability of CeA neurons[92,93]. In these rodent studies, pain-induced plasticity in the BLA deactivates the mPFC through glutamate-driven synaptic inhibition, resulting in decision-making deficits as well as depression- and anxiety-like behaviors[94,95]. This feedforward inhibition of mPFC is dependent on mGluR1/5 type of glutamate receptors[96] and the endocannabinoid system; a combined activation of cannabinoid receptor type 1 (CB1) and mGluR5 receptors will restore the mPFC activity and decrease the spinal withdrawal reflexes as well as cognitive deficits in animal pain models[97-99]. In turn, the mPFC also projects directly to the ITC to inhibit the CeA, and this top-down projection provides a critical cortical control of amygdala. In this model, restoring the mutual inhibition of the PFC and amygdala may play an important role in regulating pain

phenotypes (Figure 1). Recent human imaging studies have confirmed some of these findings, specifically the activation of the mPFC during pain state[100].

2.2.2 Prefrontal cortex - nucleus accumbens projection in acute and chronic pain regulation: The Nucleus Accumbens (NAc) has been mostly studied in the context of rewards, but it is also known to play key roles in aversion-type behaviors[101,102]. Neurons of the NAc are strongly modulated by dopamine, which are released from a neighboring region, the ventral tegmental area (VTA). Relief of aversive states, including pain, has been thought as a rewarding stimulus that activates the NAc. Accordingly, pain relief has been shown to give rise to negative reinforcement via increased dopamine inputs to the NAc[103]. Recent studies in animal pain models also demonstrate that aversion and reward prediction signals may in fact be differentially encoded by specific patterns of dopamine responses in different subregions of the NAc, the central core and the surrounding shell. In anesthetized rats, for example, painful tail pinch triggers transient dopamine release in the core region of the NAc, whereas in the shell subregion dopamine is released after the termination of the same stimulus[104]. This time course of activity in the NAc shell is consistent with the concept of pain offset as a reward. In humans, fMRI studies have demonstrated a negative BOLD signal valence in the NAc at the onset of a thermal nociceptive stimulation and a positive signal valence at the stimulus offset (relief)[105]. These studies suggest a role of the NAc as a common neurobiological center for processing pain and pleasure[106].

In addition to its regulation of the aversive component of pain, the NAc has also been shown to regulate the sensory pain pathway[107-110]. Indeed, the NAc receives nociceptive information via direct projections from spinal dorsal horn neurons[111]. Consequently, studies in animal models have demonstrated that inactivation of the NAc shell with lidocaine increases spinal withdrawal to pain, whereas dopaminergic agonist in the NAc has the opposite effects[112].

Cortical and subcortical regions including the PFC and ACC[113-115] and amygdala[91] are known to project to the NAc. Activation of the PFC-NAc circuit in animal models have been shown to provide important regulation for the sensory and aversive components of acute[116] and chronic pain[117]. In humans, in the case of chronic pain, the PFC connectivity to NAc is increased[118-120] as a potential compensatory response. It is also worth-noting that this increased functional connectivity takes place at the same time as a global decrease in PFC outputs. Chronic pain has been shown to deactivate the PFC[95], possibly due to reduced glutamatergic inputs and decreased dendritic formation of the layer 5 output cells[59,94], as well as to a diminished level of activity of the cholinergic interneurons[61]. Selectively increasing the excitatory output to the NAc can compensate for these chronic pain-induced changes, and subsequently reduce pain and associated anxiety/depressive behaviors associated with chronic pain. Thus, chronic pain may elicit a circuit-specific change in the PFC, resulting in increased projection to some areas and decreased projections to others.

2.2.3 Insula – limbic structures: Whereas prefrontal projections to the limbic system are well established, fewer studies have examined the connection between the insula and the amygdala or NAc[121,122]. It is interesting to note, however, that activities in both the NAc and the insula precede, but have opposing effects on risky choices[123], and that direct structural

connections between these two areas have been reported in humans during gambling tasks[124]. Moreover, insula glutamatergic inputs to the NAc are necessary for aversion-resistant alcohol consumption in rodent pain models[125]. Similar to the mPFC, the insula and amygdala are broadly interconnected either via direct or indirect projections[126,127]. The insula-amygdala pain pathway is involved in fear conditioning[128]. Thus, it is likely that the connection between the insular and the limbic system plays important roles in anxiety-type of behaviors as well as risk assessment to regulate pain.

3. Implications for a neuromodulatory approach for pain treatment

Chronic pain affects up to one third of Americans, and certain acute pain syndromes such as postoperative pain also carry significant morbidities. Current pharmacological treatments remain limited by side effects and suboptimal efficacy, in part due to the complexity of the neural network involved in pain processing. An improved understanding of the cortical modulation of pain can have important impact on two nonpharmacological approaches: cognitive-behavioral therapy (CBT) and neuromodulation.

In terms of psychological evaluation and treatment of chronic pain, CBT has received the most atten-tion. CBT is multifaceted and addresses mood (typically anxiety and depression), function (including disability) and social engagement, as well as indirectly targeting analgesia. A growing body of research is showing the benefits of behavioral therapy for pain management[129,130] and the effect of CBT on neurophysiological changes in the brain[131]. After an 11-week CBT program, for example, gray matter volume was increased in PFC, ACC, and sensorimotor cortices in patients with a variety of chronic pain conditions, and these changes were associated with a decrease in pain catastrophizing[132]. In patients with fibromyalgia, CBT led to increased PFC activation and PFC-thalamus functional connectivity, as well as reported improvement in function. These findings lend support to the notion that psychological treatments can impact cortical modulation of pain to exert greater control of cognitive and emotional variables related to pain[133].

In addition to CBT, more invasive neuromodulation techniques such as deep brain stimulation (DBS), transcranial direct current stimulation (tDCS), and transcranial magnetic stimulation (TMS) can also target pain-modulating centers in the brain. Currently, neuromodulation treatment for pain has been limited to spinal cord stimulation (SCS) and peripheral nerve stimulations[134]. An increasing number of studies, however, have begun to investigate the possibility to target various nuclei in the sensory thalamus, periaqueductal grey, NAc, motor cortex, ACC and PFC, for pain control[135,136]. Bilateral stimulation of ACC using a DBS protocol achieved temporary pain relief in a small study of patients, as these patients still felt pain, but “it didn’t bother” them as much[137]. In a more recent study, chronic DBS of the ACC using implanted electrodes produced analgesic effect in 30% of the patients[138]. The side effects have in general been mild in most studies [139]. Similar neuromodulatory studies using TMS to stimulate the mPFC are ongoing as well, and some studies show a decrease in pain rating in individuals experiencing thermal pain[140,141]. Finally, studies using stimulation of the motor cortex (MCS) to decrease thalamic overactivity and modulate the descending pain pathway have demonstrated mixed efficacy[142,143] in humans, despite promising results in animals[144,145]. Meanwhile,

stimulation of parietal cortex seems more specific for mechanical/tactile related pain[146,147]. In the cases of motor cortex and parietal cortex stimulation, although the underlying mechanisms are not well-understood, the approach nevertheless holds significant therapeutic promise.

Important factors to consider for cortical and subcortical stimulation include the duration of stimulation, frequency of stimulation, and the possibility of low frequency stimulation to activate neurons versus high frequency stimulation to inhibit neuronal activities. A desired outcome would be for the neuromodulation device to perform stimulation or inhibition of the neuronal networks during the occurrence of pain episodes or in a more focal way to avoid stimulation of 'en passant' fibers.

In conclusion, we know that nociceptive inputs reach multiple brain areas to give rise to the experience of pain, including sensory and emotional aspects. These circuits are under strong top down controls to regulate sensation and affect in acute and chronic states. Recent studies underscore the role of cortical and sub-cortical brain areas in the associations of psychological factors and early traumatic experiences with acute and chronic pain processing [148-151] which has potentially important clinical implications[152-154]. Future studies of the cortical and subcortical circuitry are needed to enhance our understanding of pain processing and regulation to guide the development of better analgesic therapies.

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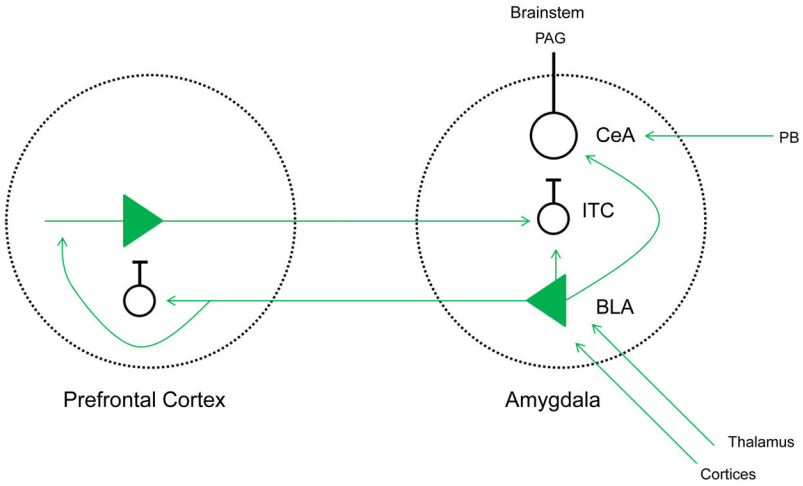

Figure 1.

The amygdala sends glutamatergic projections (green) from the basolateral nucleus (BLA) to mPFC (blue dashed box) pyramidal cells, and to mPFC GABAergic interneurons inhibiting mPFC pyramidal cells (feedforward inhibition). mPFC pyramidal cells send glutamatergic projections to GABAergic interneurons in the amygdala (intercalated cells, ITC) to control amygdala output from the central nucleus (CeA).