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Focus Article

The Dorsolateral Prefrontal Cortex in Acute and Chronic Pain

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Abstract: **The dorsolateral prefrontal cortex (DLPFC) is a functionally and structurally heterogeneous region and a key node of several brain networks, implicated in cognitive, affective, and sensory processing. As such, the DLPFC is commonly activated in experimental pain studies, and shows abnormally increased function in chronic pain populations. Furthermore, several studies have shown that some chronic pains are associated with decreased left DLPFC gray matter and that successful interventions can reverse this structural abnormality. In addition, studies have indicated that noninvasive stimulation of the left DLPFC effectively treats some chronic pains. In this article, we review the neuroimaging literature regarding the role of the DLPFC and its potential as a therapeutic target for chronic pain conditions, including studies showing the involvement of the DLPFC in encoding and modulating acute pain and studies demonstrating the reversal of DLPFC functional and structural abnormalities after successful interventions for chronic pain. We also review studies of noninvasive brain stimulation of the DLPFC showing acute pain modulation and some effectiveness as a treatment for certain chronic pain conditions. We further discuss the network architecture of the DLPFC, and postulate mechanisms by which DLPFC stimulation alleviates chronic pain. Future work testing these mechanisms will allow for more effective therapies.**

Perspective: ***The structure and function of the DLPFC is abnormal in some chronic pain conditions. Upon successful resolution of pain, these abnormalities are reversed. Understanding the underlying mechanisms and the role of this region can lead to the development of an effective therapeutic target for some chronic pain conditions.***

Key words: *Orofacial pain, pain, magnetic resonance imaging, brain function, morphometrics, treatment planning.*

Pain poses the largest health-related burden on society, and is the primary cause of long-term disability globally.[103] Despite many decades of pain research, there are few effective treatments for chronic pain. The pain experience is a construct of the central nervous system (CNS)—an emergent property of network activity in the brain[2,23,48]—and chronic pain is thought to be a CNS disorder.[98] However, there has yet to be a single brain region or network shown to be specific and sufficient for nociceptive processing and pain modulation.[42,50,83] One reason for this knowledge gap is that pain is a multidimensional experience, comprised of sensory, emotional, cognitive, and motivational components. Without a better understanding the contribution and interaction of these components, it is difficult to identify the mechanisms in an ecologically valid or clinically meaningful way. Neuroimaging techniques such as electroencephalography, magnetoencephalography,

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and functional magnetic resonance imaging provide a powerful set of tools to noninvasively investigate the CNS. Noninvasive brain stimulation paradigms, such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), offer a unique ability to temporarily and noninvasively enhance or inhibit activity within specific brain regions (ie, create a virtual lesion). Coupling neuroimaging with these stimulation paradigms can help identify causal links between brain regions and pain perception.

Despite the lack of pain specificity in the CNS, there is a set of brain regions that are consistently activated in response to experimental nociceptive stimulation,[25,57] including brainstem regions, such as the raphe and the periaqueductal gray, the thalamus, the primary and secondary somatosensory cortices, the midcingulate cortex, and the insula. Some of these regions also exhibit abnormal structure and function in chronic pain disorders, suggesting that they may be implicated in nociceptive processing and/or pain modulation.[2,16,23] Although the pattern of gray matter abnormalities is not necessarily consistent across all chronic pain disorders, there appears to be some level of convergence across different chronic pain disorders. For example, patients with chronic back pain,[3,79,85,92] migraine,[44,77,102] trigeminal neuropathic pain,[22] hypnic headache,[37] chronic post-traumatic headache,[64] hip osteoarthritis,[78,79] and complex regional pain syndrome[26] have reduced dorsolateral prefrontal cortex (DLPFC) gray matter, compared with healthy subjects (for a comprehensive review, see Davis and Moayedi[23]).

DLPFC Function

The DLPFC is a large and functionally heterogeneous brain region (Fig 1).[31] Compared with other primates, the DLPFC is substantially expanded in humans, suggesting a role in complex cognitive processes.[62,73] The DLPFC spans over several Brodmann areas (BAs), including BAs 9, 8a, 8b, and the dorsal part of 46.[82] Posteriorly, it is banked by the precentral gyrus, and spans the middle frontal gyrus, the superior frontal sulcus, and the lateral aspect of the superior frontal gyrus (Fig 1). The anterior bank is inconsistently defined across the literature, with perhaps the best delineation being marked by frontopolar cortex (BA 10).[45,67,68] Neuroimaging studies of 2 main types have been essential to our understanding of DLPFC function: studies of resting state connectivity (ie, in the absence of an overt task), which reveal the architecture of intrinsic brain networks[8,21,74,94]; and studies involving task performance or perception, where the precise location, intensity, and time-course of DLPFC activation depends substantially on the type of task (Fig 1).

Although the DLPFC has been implicated in many important brain functions (Fig 2), and its role remains a topic of debate in the literature, it is generally associated with maintenance and regulation of top-down modulation, and driving appropriate behavioral responses.[69,82] However, it has also been shown to be involved in cognitive processes,[18,43,62,96] such as attention,[6,104-106]

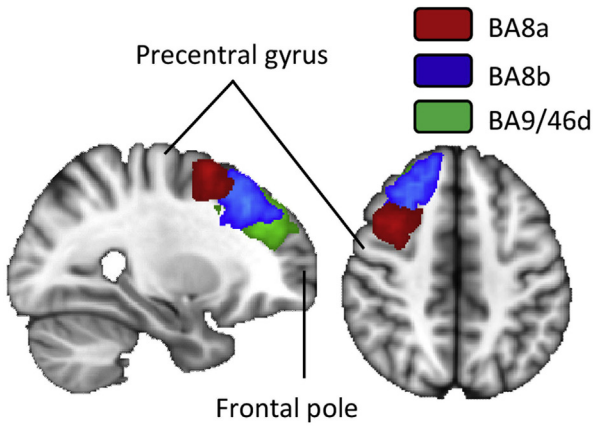

Figure 1. Regions of the brain comprising the DLPFC, including BAs 8, 9, and the dorsal part of 46. The 3 clusters shown represent subregions of the DLPFC on the basis of a parcellation scheme by Sallet and colleagues.[82] The DLPFC is a large, heterogeneous brain region spanning the middle frontal gyrus and the lateral aspects of the superior frontal gyrus. It is banked by the inferior frontal sulcus on the lateral side, the precentral sulcus on the posterior bank, and the frontal polar cortex on the anterior bank.

value encoding,[11,40,46,52,95] working memory,[5] creativity,[53] decision-making,[71,73] and emotional regulation.[15,27,29,66,99]

The DLPFC is also often activated in pain neuroimaging. Notably, it is not the only region activated, as described previously, but may be a key node of networks implicated in nociceptive processing and pain modulation (Fig 2). Specifically, it shows activation in response to nociceptive stimuli in healthy subjects, or shows differential activation between chronic pain patients and control subjects. Its role in pain remains ambiguous: it has been shown to be involved not only in pain suppression, in line with its role in cognitive and emotional control, but also in pain detection. In support of the former hypothesis, a study reported that left DLPFC activity was negatively related to pain unpleasantness (the extent to which pain bothers the subject).[56] Additional support for the role of DLPFC in pain suppression hypothesis comes from studies that have reported the DLPFC to be involved in placebo modulation of pain.[70,107] The role of DLPFC in pain detection, however, is supported by the observation that the DLPFC exhibited binary (all or none) activity in response to pain in a sample of healthy subjects, regardless of the stimulus or reported pain intensities.[10] In contrast to these pain detection and suppression hypotheses, neuroimaging studies of experimental persistent pain, and experimental models of hyperalgesia and allodynia have shown a parametric relationship between pain sensitization and DLPFC activity,[41,55,87] suggesting a role in pathological pain.

Several lines of evidence support a role for the DLPFC in the suppression of pain and maintenance of pain inhibition. For example, subjects given instructions to suppress pain show increased activation of bilateral—but particularly the left—DLPFC during prolonged acute

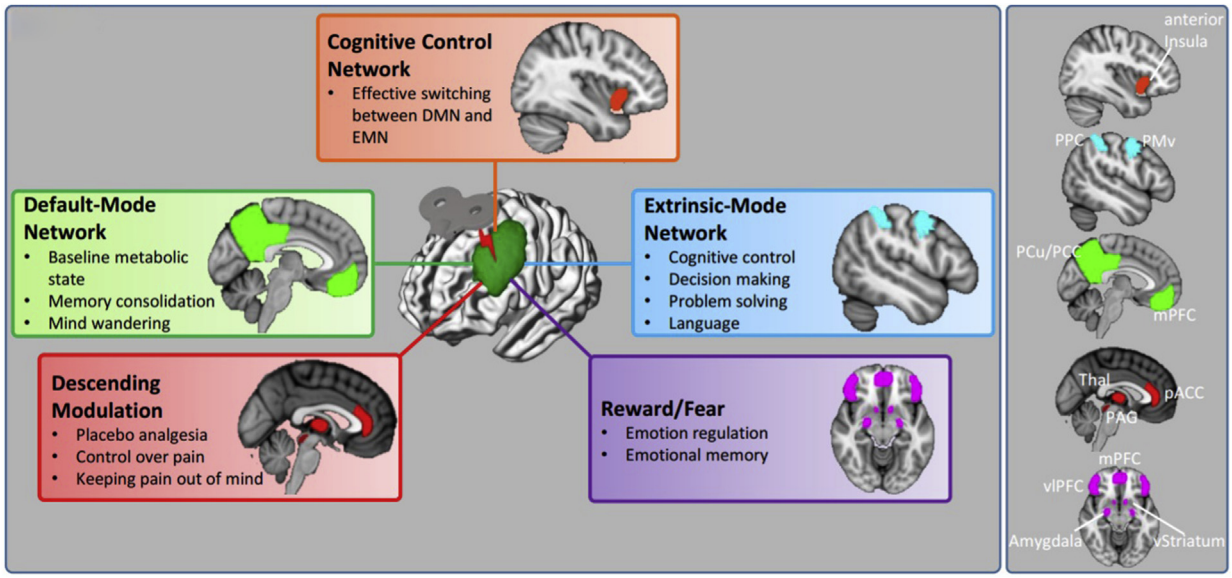

Figure 2. The DLPFC is a large, heterogeneous cortical region shown in green on a standard brain. The DLPFC is involved in multiple processes, and although it has been implicated in pain regulation, the mechanisms are unclear. Here we outline how the DLPFC could affect pain through several networks, including: controlling the regulation of cognitive networks (cognitive control network) through effective switching of the DMN and EMN; enhancing activity in a network involved in descending modulation of pain; reducing emotional reactivity to pain through reward/fear circuitry. Some studies have also provided evidence of effectiveness of the left DLPFC stimulation to treat chronic pain. The right panel provides the labels of the brain regions within each of these networks. Abbreviations: PPC, posterior parietal cortex; PMv, ventral premotor cortex; PCu/PCC, precuneus/posterior cingulate cortex; mPFC, medial prefrontal cortex; Thal, thalamus; pACC, pregenual anterior cingulate cortex; PAG, periaqueductal gray; vlPFC, ventrolateral prefrontal cortex; vStriatum, ventral striatum.

pain stimulation.[30] Bilateral DLPFC activation was associated with reduced unpleasantness of thermal pain.[56] Studies on placebo analgesia have also shown a role of DLPFC in pain suppression, and inhibiting DLPFC activity could block the placebo response.[47] In support of these findings, the DLPFC has been implicated in integrating incoming nociceptive signals with the expectation of pain[4]—a key feature of placebo analgesia. Furthermore, perceived control of pain was associated with activation of the right DLPFC.[109] Relatedly, Brascher et al reported that uncontrollable pain resulted in increased activation of pain-related areas including the thalamus and insula, but that bilateral DLPFC had increased negative connectivity strength during controllable pain to the thalamus as well as the right anterior insula.[12] In other words, the DLPFC suppressed insula and thalamus activity and reduced pain sensitization associated with uncontrollable pain. Finally, the connectivity between the left and right DLPFC has been linked to individual pain sensitivity, such that stronger interhemispheric connectivity was associated with greater pain tolerance.[93]

There is converging evidence that the DLPFC has a role in cognitive components of the pain experience. As mentioned previously, studies in which participants are given a sense of controllability over nociceptive stimuli have suggested that the DLPFC is involved in cognitive control over pain.[75,109] Consistent with this finding, pain-related activity within the bilateral DLPFC is negatively correlated with pain catastrophizing, a measure of maladaptive pain cognitions, and a sense of uncontrollability, indicating a role of DLPFC in pain-coping.[88] Cognitive control can reduce pain and has in part been attributed to a brain network comprising prefrontal regions including the DLPFC, ventrolateral prefrontal cortex, and orbitofrontal cortex, anterior insula, anterior cingulate cortex, and brainstem regions, such as the periaqueductal gray and the rostral ventral medulla.[7] Furthermore, activation of part of this circuit, including the DLPFC, anterior cingulate cortex, and cerebellum, has been implicated in mediating the analgesic effects of spinal cord stimulation in chronic back pain patients,[59] suggesting that peripheral and central mechanisms may interact to reduce pain. In sum, these studies suggest that the DLPFC acts as an interface between cognitive processing and pain regulation.

It is noteworthy, however, that functions should not be attributed to single brain regions in isolation. In this regard, the DLPFC is a key node of at least 3 brain networks: it sits between the interface of the extrinsic mode network (EMN)[39] and default mode network (DMN),[28,74] and it is a key node in the cognitive control network.[19] The EMN is thought to be a generalized network allocating cognitive resources to any cognitive task or sensory processing of the external milieu. The DMN, on the other hand, is active in the absence of any overt stimulus or task, and is thought to be related to monitoring of the internal milieu and introspection. In fact, it is believed that the DLPFC acts as a switch and interface between the EMN and the DMN.[86] It is important to understand that pain is a multidimensional experience and, thus, must be the product of complex network interactions between brain regions, and that this activity can interact and modulate other networks. This has been shown in a study examining pain–

cognition interactions, which reported that acute experimental pain increased activity in a network modulated by cognitive load—the EMN.[89] More specifically, the study reported that when subjects performed a cognitive task while they received a painful stimulus, there was increased activity of in the ventrolateral part of the DLPFC, and deactivation of a more dorsomedial part of DLPFC that is associated with the DMN. Greater activation of the EMN or less deactivation of the DMN during task performance could be an effect of resource competition, in which cognitive processing is limited by the availability of circuits supporting those functions.[63] These limited cognitive resources could then affect top-down modulation requiring active control over pain. These studies suggest that targeting the DLPFC activity and connectivity could be used to design interventions for reducing pain.

Abnormal DLPFC Structure in Chronic Pain

Further evidence for a role of the DLPFC in pain processing comes from studies investigating the structure and function of the brains of patients with chronic pain.[23] For example, patients with idiopathic temporomandibular disorders had decreased white matter connectivity from the midcingulate cortex to the DLPFC, compared with control participants,[58] and abnormally increased left DLPFC activity during an emotional counting Stroop task.[108] One study that contrasted brain resting cerebral blood flow between 2 chronic orofacial pain disorders, temporomandibular disorders and trigeminal neuropathic pain, reported that both patient groups had increased DLPFC resting cerebral blood flow compared with pain-free control participants, suggesting that spontaneous pain is related to DLPFC activity.[111] Other studies have reported lower gray matter volume (GMV) or thinner cortices in the DLPFC in patients with chronic pain, including those with irritable bowel syndrome,[9,90] chronic low back pain,[3,85,92,110] migraine,[38] trigeminal neuralgia,[35,65] chronic post-traumatic headache,[64] and complex regional pain syndrome.[26] In some cases, these structural abnormalities were correlated with pain catastrophizing or other clinical characteristics.[38] These findings are corroborated by magnetic resonance spectroscopy studies that have found decreased levels of N-acetyl-aspartate—a putative measure of neuronal viability—in the DLPFC in chronic back pain[32] and complex regional pain syndrome.[33] In some cases, these structural abnormalities were correlated with pain catastrophizing or other clinical characteristics.[38] Therefore, it is feasible that the gray matter reductions observed are related to neuronal loss in the DLPFC, although that does not preclude other potential cellular and molecular mechanisms.[23,72]

In terms of functional connectivity studies of chronic pain, only a handful of studies have reported abnormal DLPFC connectivity. One study reported that chronic migraine patients had reduced connectivity of bilateral DLPFC to nodes of the DMN.[38] Notably, this connectivity was negatively correlated with pain catastrophizing. Two studies reported abnormal DLPFC connectivity to various brain regions in chronic back pain.[17,36] Additionally, aberrant DLPFC activity can predict treatment outcomes in fibromyalgia,[84] and such abnormalities appear to normalize after successful intervention. Chronic low back patients showed a lack of deactivation of the DLPFC while performing a cognitive task, which resolved after effective treatment.[92] Patients also had abnormal DLPFC connectivity to the DMN and the EMN.[17] These studies suggest that normalization of the left DLPFC function could reflect recovery of cognitive ability, potentially including cognitive coping that could help reduce pain. Furthermore, DLPFC connectivity can help direct patients into different health care streams and effectively allocate these resources.

Although chronic pain is associated with decreased GMV in many cortical and subcortical brain regions, there is growing evidence that these structural changes are partially reversed with alleviation of the pain through interventions or spontaneous resolution. Several of these studies showed partial recovery of the left DLPFC gray matter. For example, one study reported an increase in left DLPFC brain gray matter in chronic back pain patients 6 months after spinal surgery or facet joint block compared with before treatment.[92] This normalization of DLPFC gray matter correlated with a reduction in clinical pain intensity and reduced disability. Other studies reported normalized GMV in the right DLPFC after total knee replacement,[78] and normalized left DLPFC GMV 1 year after onset of post-traumatic headache, which corresponded with a resolution of headache pain.[64] Another study investigating the neural underpinnings of effective pain management with cognitive behavioral training in a mixed chronic pain population reported increased left DLPFC GMV, which correlated with a reduction in pain catastrophizing.[91] Another study reported reduced DLPFC GMV in pediatric patients with complex regional pain syndrome, among other brain regions, that were reversed with treatment.[26] Notably, there was increased functional connectivity between the DLPFC and the periaqueductal gray—an opioid-rich brainstem region involved in descending pain modulation.[91] These studies suggest that the DLPFC structure could be a marker of successful intervention for pain conditions. However, an outstanding question is the cellular and molecular basis of structural plasticity in pain. Evidence from learning and memory studies in rodents reveal a role for neuroplasticity—either related to neurogenesis, or neural reorganization.[51,81] In contrast, positron emission tomography imaging studies in humans,[54] as well as electrophysiological and immunohistochemical studies in rodent pain models, suggest a prominent role for glial cells[100] or other immune cells.[80] A recent study reported that reductions in GMV in fibromyalgia were associated with reductions in water content, not neural loss.[72] However, the same study reported that increases in gray matter were associated with an increase of a proxy index of neurons, suggesting neural growth. These questions must be answered by investigating the histological basis of magnetic resonance imaging-detectable plasticity to better understand what such structural changes in the brain represent, and to

develop novel therapeutic targets. Another important consideration is that the changes observed in the DLPFC may not be directly related to pain, but may be secondary to the resolution of chronic pain. For example, several studies have shown the DLPFC to be an excellent therapeutic target for managing and treating major depressive disorder.[24] It is therefore possible that studies that have reported effective chronic pain treatment by DLPFC stimulation could be related by treating comorbidities (ie, these treatments could be treating depression), which then alleviates pain. Alternatively, depression as well as chronic pain may share some common neural substrates, such as the DLPFC. However, because of how little is known about these mechanisms, an essential step toward developing new chronic pain management tools is to better characterize structural plasticity.

The DLPFC as a Therapeutic Target

Because of the compelling evidence that DLPFC structure and function reflect chronic pain states, and because the DLPFC is implicated in pain regulation, it is feasible that this brain region could potentially serve as a therapeutic target. Indeed, several studies have now shown that noninvasive brain stimulation of this region can effectively manage pain—either acute or chronic pain.[14,34,76]

Specifically, rTMS of the left DLPFC has shown promise as a treatment for various chronic pain disorders, including migraine[14,20] and burning mouth syndrome.[101] rTMS studies for other chronic pains have been reviewed elsewhere,[60] and include other cortical targets, such as the primary somatosensory and motor cortices.[49] In healthy participants, rTMS of the left DLPFC reduces spontaneous pain from capsaicin application,[13] and this effect has been shown to occur via an opioid-dependent mechanism (ie, it is blocked by naloxone).[97] Another type of noninvasive brain stimulation—tDCS—of the left DLPFC in healthy participants has also been shown to increase pain tolerance and improve performance in a cognitive task, consistent with the DLPFC's role in cognitive and pain modulatory processes.[61] Notably, this does not suggest that the same region of the DLPFC is responsible for both functions, but rather the lack of specificity of tDCS—it stimulates large swathes of the cortex. Nonetheless, several studies have reported on the efficacy of left DLPFC rTMS for the treatment of major depression,[49] which alone might be useful for chronic pain patients via improved quality of life and an increase of health-promoting behaviors, such as increased physical exercise, social interactions, and active engagement in pain-reducing strategies. Altogether, there is good evidence supporting the potential for the DLPFC as a target for therapeutic intervention in chronic pain conditions. These effects could be mediated by descending modulatory (opioidergic) systems, or effects on cognitive or affective aspects of the pain experience, or a combination of these mechanisms. Future work should investigate the consistency of DLPFC activity in response to experimental pain, and the consistency of structural and functional DLPFC abnormalities in chronic pain conditions.

There are other interventions that have been shown to regulate DLPFC activity, such as mindfulness meditation.[1] A recent study has shown that mindfulness meditation is effective at reducing experimental heat pain.[112] This study reported a significant deactivation of the DLPFC during nociceptive stimulation and an increase in ventrolateral prefrontal cortex and orbitofrontal cortex activation, compared with sham meditation and placebo pain modulation. Alternative, noninvasive treatments that can be used to regulate DLPFC function may be preferred by some patients, because they are associated with few adverse side effects. However, future work is required to directly investigate how these techniques regulate pain.

In sum, although the DLPFC has many functions, and is by no means pain-specific, imaging and brain stimulation can be used to tap its regulatory effects to modulate and manage chronic pain.

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