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Minireview

Targeting Prefrontal Cortex Dysfunction in Pain

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ABSTRACT

The prefrontal cortex (PFC) has justifiably become a significant focus of chronic pain research. Collectively, decades of rodent and human research have provided strong rationale for studying the dysfunction of the PFC as a contributing factor in the development and persistence of chronic pain and as a key supraspinal mechanism for pain-induced comorbidities such as anxiety, depression, and cognitive decline. Chronic pain alters the structure, chemistry, and connectivity of PFC in both humans and rodents. In this review, we broadly summarize the complexities of reported changes within both rodent and human PFC caused by pain and offer insight into potential pharmacological and nonpharmacological approaches for targeting PFC to treat chronic pain and pain-associated comorbidities.

SIGNIFICANCE STATEMENT

Chronic pain is a significant unresolved medical problem causing detrimental changes to physiological, psychological, and behavioral aspects of life. Drawbacks of currently approved pain therapeutics include incomplete efficacy and potential for abuse producing a critical need for novel approaches to treat pain and comorbid disorders. This review provides insight into how manipulation of prefrontal cortex circuits could address this unmet need of more efficacious and safer pain therapeutics.

Introduction

Pain is a multidimensional experience making it more than a sensation detected by the peripheral nervous system. It engages the central nervous system via multiple cortical and subcortical networks. Human brain imaging shows that pain activates multiple regions of the cortex including primary and secondary somatosensory cortices and the prefrontal cortex (PFC) (Rainville et al., 1997; Apkarian et al., 2005; Bushnell et al., 2013). Neurons in the PFC respond to noxious (i.e., painful) stimuli (Condes-Lara et al., 1989) and play an important role in the emotional valence, attentional components, and the descending modulation of pain (Porro et al., 2002; Lee et al., 2015; Martinez et al., 2017; Dale et al., 2018; Zhou et al., 2018a). Reduced PFC activity is implicated in affective and cognitive disturbances associated with chronic pain (Millecamps et al., 2007; Ji et al., 2010; Cardoso-Cruz et al., 2013; Lee et al., 2015; Wang et al., 2015). Recent evidence shows that negative affect, commonly associated with both chronic pain and PFC function, should be considered in the development of effective pain therapies (Wasan et al., 2015; Edwards et al., 2016). Here, we review PFC circuits as a contributor to both sensory and affective pain and as a potential target for pain therapy.

Pain-Induced Disruptions within Rodent PFC

Early pivotal work in mice showed that both chronic inflammatory pain and neuropathic pain enhance excitatory synaptic transmission in the anterior cingulate cortex (ACC), a subregion of the PFC (Zhao et al., 2006; Xu et al., 2008). A short time later, a novel study in the rat showed that the spared-nerve injury (SNI) model of neuropathic pain (Decosterd and Woolf, 2000) induced increases in dendritic complexity and *N*-methyl-D-aspartate (NMDA)/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) current ratios in layer 2/3 PFC neurons (Metz et al., 2009). Another study showed that neuropathic pain enhanced the excitability of an intrinsically distinct subclass of ACC-PFC neurons (Cao et al., 2009).

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ABBREVIATIONS: ACC, anterior cingulate cortex; ACh, acetylcholine; BBB, blood–brain barrier; DBS, deep brain stimulation; DLPFC, dorsolateral prefrontal cortex; Dyn, dynorphin; IL-PFC, infralimbic region of prefrontal cortex; KOR, κ opioid receptor; L5, layer 5; mGluRs, metabotropic glutamate receptors; M1, muscarinic subtype receptor 1; NMDA, *N*-methyl-D-aspartate; PAG, periaqueductal gray; PFC, prefrontal cortex; PL-PFC, prelimbic region of prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation; SNI, spared-nerve injury; tDCS, transcranial direct current stimulation; tFUS, transcranial focused ultrasound; TLS, transcranial laser stimulation.

Increased excitability of ACC-PFC neurons following nerve injury was later reported to result from cortical disinhibition caused by reduced connectivity between pyramidal neurons and inhibitory interneurons in the ACC (Blom et al., 2014). Recent work shows that increased activity of the ACC-PFC in mice is involved in maintenance of chronic pain and defensive behaviors to painful stimuli (Lee et al., 2022). Together, these findings indicated that chronic pain creates a state of hyperexcitability within the PFC.

Work around the same time implementing magnetic resonance imaging of brains from rats with prolonged nerve injury pain (>4 weeks) revealed a significant decrease in volume across multiple cortical regions including the PFC, which coincided with emergence of anxiety-like behaviors (Seminowicz et al., 2009). It was later reported that cognitive deficits associated with arthritic pain are associated with increased polysynaptic inhibition of layer 5 (L5) pyramidal neurons in the prelimbic region of the PFC (PL-PFC), which was driven by signaling through metabotropic glutamate receptors (mGluRs) (Ji et al., 2010; Sun and Neugebauer, 2011). Work from Zhang et al. (2015) supported these findings by showing that nerve injury in mice increases excitatory input to parvalbumin-positive inhibitory neurons in PL-PFC, consequentially decreasing excitability of L5 pyramidal neurons. Our later work corroborated these results by showing that SNI enhances intrinsic and excitatory synaptic activity of L5 parvalbumin-positive inhibitory neurons in PFC of male, but not female, mice (Jones and Sheets, 2020).

In rats, SNI impairs glutamatergic synaptic signaling and decreases dendritic length in L5 PFC pyramidal neurons (Kelly et al., 2016). Work from our laboratory showed that the chronic constriction injury model of neuropathic pain, which is similar to SNI, enhances the inhibitory–excitatory balance of local inputs onto PL-PFC pyramidal neurons that project to the periaqueductal gray (PAG), a key structure in the descending analgesic system (Cheriyan and Sheets, 2018). Interestingly, this led to reduced intrinsic excitability of PAG-projecting neurons in the PL-PFC but not in the infralimbic region of prefrontal cortex (IL-PFC) (Cheriyan and Sheets, 2018), supporting the notion that decreased output from L5 PL-PFC contributes to pain expression. Indeed, restoring basal activity of PL-PFC neurons using optogenetic stimulation alleviates sensory and affective pain behaviors in rats with chronic inflammation in the hindpaw (Dale et al., 2018). Huang et al. (2019) then reported downregulation of cannabinoid receptor 1 mRNA in PL-PFC of SNI mice and showed that SNI enhances feedforward inhibition of PAG-projecting neurons in the PL-PFC, which leads to a disruption of descending PAG modulation of noradrenergic and serotoninergic circuits in the spinal cord. In a recent spatial transcriptomic dissection of the mouse PFC, it was revealed that a specific subtype of PL-PFC L5 extra-telencephalic neurons with robust projections to the PAG were the most transcriptionally perturbed by SNI (Bhattacherjee et al., 2023). This collection of consistent findings in the mouse indicates that a significant component of chronic pain pathophysiology involves the attenuation of PFC-PAG pathway activity.

Our recent work demonstrates that both SNI and the plantar incision model (PIM) of surgical pain enhances the excitability of layer 2/3 PL-PFC neurons expressing dynorphin (Dyn), which is the endogenous opioid ligand for the κ opioid receptor (KOR) (Zhou et al., 2023). KORs mediate the sensory (Obara et al., 2003; Xu et al., 2004; Aita et al., 2010) and negative affective component of pain (Cahill et al., 2014; Massaly et al., 2019; Navratilova et al., 2019). Both Dyn and KOR mRNA are upregulated in the PFC of chronic pain mice (Candeletti and Ferri, 1995; Palmisano et al., 2019; Bhattacherjee et al., 2023) suggesting that Dyn-KOR signaling within PFC circuits regulates to pain-induced affective behaviors. Indeed, infusion of the synthetic KOR agonist U50,488 or Dyn analog E-2078 into the PFC evokes conditioned place aversion in rats (Bals-Kubik et al., 1993). In addition, KOR antagonism with norbinaltorphimine in the PFC promotes anxiolytic behavior (Tejeda et al., 2015). The KOR agonist U69,593 selectively inhibits glutamatergic basolateral amygdala inputs to the PFC (Tejeda et al., 2015), which is a pathway (i.e., basolateral amygdala-PFC) known to be disrupted in various preclinical pain models (Ji et al., 2010; Kiritoshi et al., 2016; Huang et al., 2019; Cheriyan and Sheets, 2020). Together, this infers that local release of Dyn into the PFC due to hyperactivity of PL-PFC-Dyn+ neurons is a signaling pathway that mediates aversion and negative valence/affect associated with pain.

Relevance of Rodent Models to the Human Chronic Pain

Translation of how anatomic and functional changes to PFC circuits in rodent pain models correlates with pain-induced disruption of the human PFC is still evolving. One major hurdle remains the obvious lack of conscious reporting by rodents regarding ongoing pain and the affective aspect of pain. However, the use of place preference paradigms has emerged as a novel method for assessing spontaneous pain and the aversive component of pain in rodents (Johansen et al., 2001; King et al., 2009; Navratilova et al., 2013). Many studies using place preference describe a significant role of PFC activity in modulating affective pain (Johansen et al., 2001; Lee et al., 2015; Navratilova et al., 2015; Huang et al., 2019). Another limitation is that rodent PFC does not have a granular anatomy observed in human PFC (Preuss, 1995; Laubach et al., 2018). Yet, it is argued that the rodent PL-PFC is homologous with the pregenual ACC in humans (Vogt and Paxinos, 2014; Laubach et al., 2018), which is a region associated with the unpleasantness of pain perception (Ploner et al., 2002; Kulkarni et al., 2005). There are also consistencies regarding the role of the rodent ACC-PFC and human ACC in pain regulation. Lesion of the rostral ACC-PFC attenuates of aversiveness of nerve-injury induced neuropathic pain in rats (Qu et al., 2011). This is consistent with the positive effects observed in human chronic pain patients following cingulotomy (Sharim and Pouratian, 2016; Strauss et al., 2017; Wang et al., 2017; Deng et al., 2019).

Identifying specific cellular and synaptic disruptions that drive neural connectivity changes in the PFC of human pain patients remains challenging, which highlights the importance of rodent PFC research. Progressive methods aimed at researching neural circuits in rodent models provide a unique opportunity to understand the functionality of brain networks that integrate both normal and pathologic pain input in mammals. Mice continue to be a powerful model for addressing significant aspect of these unknowns as the ability to modify murine genetics for identification and manipulation of defined circuit pathways is extremely valuable. Further, there are

numerous disease models in mice available for further exploration of the PFC network as it relates to various pain and comorbid emotional disorders.

Cortical Disruptions in Human Chronic Pain

The PFC is involved in the sensing of acute painful stimuli (Sakuma et al., 2014; Ong et al., 2019), with both the ACC-PFC and dorsolateral PFC (DLPFC) being activated by noxious stimulation (Hutchison et al., 1999; Nir et al., 2008). In addition, activation of the PFC is correlated with both anticipation and unpleasantness of pain (Lorenz et al., 2002; Porro et al., 2002). PFC activity is also implicated in anxiety and depressive symptoms associated with pain (Ochsner et al., 2006; Schweinhardt et al., 2008). In a systematic review from 2005, Apkarian et al. (2005) highlighted that although the perception of experimental pain in healthy subjects involves more frequently the ACC as well as sensory and thalamic regions, chronic pain patients show a reduced activity within these regions together with an increased activation of the PFC. Enhanced PFC activity is a neural signature of high intensity pain in chronic back pain patients (Baliki et al., 2006). Interestingly, a recent meta-analysis of functional neuroimaging studies on the effect of chronic pain treatment found that in the majority of studies, the ACC showed significantly decreased activity after chronic pain treatment in functional magnetic resonance imaging and positron emission tomography studies, whereas activity in the PFC was inconsistent (Kim et al., 2021).

Although discrimination of pain intensity is modulated by a ventrally directed pathway including diverse prefrontal cortical regions, spatial discrimination of pain stimuli involves a dorsally directed pathway that activates the DLPFC (Oshiro et al., 2009). The interpretation of a noxious stimulus intensity and its subjective perception as pain is thereby guided by γ oscillations in the PFC (Schulz et al., 2015; Nickel et al., 2017). Interestingly, at this level of the pain pathway, no lateralization occurs based on the side of stimulation. Sensitization to a painful stimulus further increases the activity of brain regions including the DLPFC (Benson et al., 2015), whereas increased pain sensitivity is associated with a decreased activity of the ventrolateral PFC and the ACC-PFC (Karshikoff et al., 2016).

Although Teutsch et al. (2008) showed that repetitive painful stimulation leads to a substantial increase of gray matter in pain-related areas for the duration of stimulation, it is well established that pain chronification has the exact opposite effect. Atrophy of PFC gray matter is detected in humans with complex regional pain syndrome, low back pain, and fibromyalgia (Apkarian et al., 2004; Kuchinad et al., 2007; Geha et al., 2008; Yuan et al., 2017). In chronic back pain patients, gray matter volume in the left DLPFC, ventrolateral PFC, and ACC-PFC shows a weak negative correlation with back pain intensity (Fritz et al., 2016), and complex regional pain syndrome duration and intensity were negatively correlated with DLPFC volume (Barad et al., 2014). Although thinning of gray matter is referred to as atrophy in many studies, thereby suggesting a reduction of neuronal cells, the decrease of gray matter in the ACC-PFC, DLPFC, and other pain-associated regions is at least in part reversible when the pain is successfully treated (Rodriguez-Raecke et al., 2009; Seminowicz et al., 2011; Seminowicz and Moayedi, 2017).

Cerebral blood flow, which is an indirect measure of neuronal activity, was reduced in the left DLPFC in a human experimental pain model of noxious heat stimulation (Nishigami et al., 2010). Initial studies investigating cerebral blood flow induced by noxious heat stimulation showed that patients with atypical facial pain showed increased blood flow in the ACC and decreased blood flow in the PFC (Derbyshire et al., 1994), whereas rheumatoid arthritis patients showed reduced blood flow in the ACC-PFC (Jones and Derbyshire, 1997). In patients with chronic neuropathic or non-neuropathic orofacial pain, only non-neuropathic chronic pain patients showed increased baseline blood flow in the ACC-PFC and DLPFC (Youssef et al., 2014), whereas chronic low back pain showed reduced blood flow in the bilateral PFC (Nakamura et al., 2014). Although inconsistent in different patient groups, changes in blood flow in response to noxious stimulation and pain chronification may be related to both loss of gray matter as well as changes in activation of the affected brain regions.

Human sexual dimorphism in pain experience and chronic pain is well-established (Unruh, 1996; Berkley, 1997; Riley et al., 1998; Mogil and Bailey, 2010; Mogil, 2012, 2020) with prevalence of chronic pain reported higher in women compared with men (Fillingim et al., 2009; Nahin, 2015; Dahlhamer et al., 2018). Although subjective pain unpleasantness was strongly associated with increased pain-evoked activation of the perigenual ACC in women (Derbyshire et al., 2002; Straube et al., 2009; Girard-Tremblay et al., 2014), men showed decreased ventromedial PFC activity (Girard-Tremblay et al., 2014). Sex differences were also found in the functional connectivity of insular subdivisions with median- and paracingulate regions and right rostral ACC (Dai et al., 2018), as well as ACC-amygdala and ACC-PAG connectivity in aged individuals (Monroe et al., 2018). This is in line with sex differences found in glutamatergic transmission in the mPFC of mice (Jones and Sheets, 2020; Knouse et al., 2022). In addition to sex differences, inter-individual differences in pain sensing are among others related to variability of pain-induced PFC activation (Coghill et al., 2003; Piche et al., 2010), inter-hemispheric connectivity of DLPFC (Sevel et al., 2016), medial-frontal and frontal-parietal network connectivity profiles (Tu et al., 2019), or gray matter volume in several brain regions, including the posterior cingulate cortex and orbitofrontal PFC (Elsenbruch et al., 2014). A continued effort to dissect sex and inter-individual differences in PFC involvement in chronic pain pathology is critical, as currently approved pain therapeutics do not account for these variables, which limits the implementation of personalized treatment strategies.

Targeting the PFC for Pain Relief

Collectively, both human and rodent studies validate that disruption of PFC circuit function is a key factor in both chronic pain and affective comorbidities associated with chronic pain, which needs to be considered when developing novel and more efficacious pain therapies (Wasan et al., 2015; Edwards et al., 2016). Therefore, what strategies can be implemented for targeting PFC circuits in chronic pain patients?

Pharmacological Interventions to Treat PFC Dysfunction Caused by Pain

The most convenient way to target the PFC for treating both sensory and affective pain is pharmacological therapeutics. Several studies have shown that pharmacological

compounds can attenuate pain symptoms through their actions in the PFC. Intracranial infusion of D-cycloserine, a partial agonist for the NMDA receptor, into the PFC significantly reduced pain behaviors in SNI rats (Millecamps et al., 2007) indicating restoration of NMDA activity in PFC as a strategy for pain relief. However, partial agonists also serve to dampen activity without complete inhibition of receptors, suggesting that reduction of NMDA receptor activation in PFC can attenuate pain. Indeed, previous work showed that NMDA receptors containg the subunit 2B (NR2B receptors) are upregulated in ACC-PFC following induction of peripheral inflammation in mice and that direct infusion of the NR2B receptor antagonists Ro 25-6981 or Ro 63-1908 into ACC-PFC reduced pain behaviors caused by inflammation (Wu et al., 2005). Injection of the fatty acid palmitoylethanolamide, which is a member of the extended endocannabinoid family and a ligand at non-cannabinoid peroxisome proliferator-activated receptors (PPAR-α), into PFC reduced mechanical allodynia in mice 30 days after nerve-injury (Guida et al., 2015). Interestingly, palmitoylethanolamide reduced expression of NR2B subunits in the PFC, which supports the notion that targeting NR2B receptor signaling in the PFC may be an effective strategy for treating chronic pain (Wu and Zhuo, 2009).

Administration of the positive allosteric modulator for mGluR5 VU0360172 together with the cannabinoid receptor 1 agonist ACEA into the IL-PFC reduces pain-related behaviors and improves cognition in arthritic rats (Kiritoshi et al., 2016). Interestingly, injection of these same compounds into the ACC-PFC did not improve symptoms of arthritic rats (Kiritoshi et al., 2016), which is one of many findings indicating that circuits across different subregions of the PFC (i.e., ACC, PL, and IL) play distinct roles in regulating responses to noxious stimuli and chronic pain (Mitric et al., 2019; Kummer et al., 2020; Tan and Kuner, 2021). Cholinergic signaling has also been shown to be disrupted in the PFC of SNI rats. Specifically, L5 PL-PFC neurons show decreased sensitivity to acetylcholine (ACh) following SNI, which is mediated by loss of signaling through the muscarinic subtype receptor 1 (M1), leading to neuronal hypoexcitability (Radzicki et al., 2017). Although not tested in a pain model, injection of the M1 agonist McN-A-343 into the ACC-PFC increases nociceptive mechanical threshold in rats (Koga et al., 2017). This implies that activation of M1 in PL-PFC may restore excitability of L5 neurons to promote analgesia, which is consistent with extensive evidence that the activity of L5 PL-PFC neurons is suppressed in chronic pain states (Ji and Neugebauer, 2011; Lee et al., 2015; Wang et al., 2015; Zhang et al., 2015; Cheriyan and Sheets, 2018; Huang et al., 2019; Mitric et al., 2019; Cheriyan and Sheets, 2020). However, targeting cholinergic signaling for pain relief extends broadly outside the PFC (Naser and Kuner, 2018).

Interestingly, administration of the antidiabetic drug metformin alleviates mechanical hypersensitivity observed in nerve-injured mice (Melemedjian et al., 2011; Inyang et al., 2019). Positive effects of metformin are also observed in models of surgical, inflammatory and chemotherapy induced pain (Russe et al., 2013; Mao-Ying et al., 2014; Burton et al., 2017). Although the effects of metformin are believed to be primarily peripheral, one reported mechanism of action for metformin is reversing reductions in axon initial segment length of IL-PFC neurons detected in SNI male mice (Shiers et al., 2018). Metformin also reverses significant declines in cognitive flexibility that is only observed in SNI male mice (Shiers et al., 2018). Given the strong association of executive function and PFC circuits (Miller, 2000), there may be therapeutic potential in repurposing metformin for targeting PFC dysfunction and cognitive deficits caused by chronic pain, which is a significant problem in human pain patients (Eccleston, 1995).

Ketamine is a general anesthetic that produces a cataleptic state termed dissociative anesthesia but can also produce significant analgesia (White et al., 1982) and positive effects on mood (Berman et al., 2000; Zarate et al., 2006). Innovative work from Zhou et al. (2018b) showed that ketamine produces a robust reduction in aversion caused by inflammatory pain in rats and this effect involves reducing pain-induced hyperactivity of the ACC-PFC. Later work indicated that anti-aversive effects of ketamine are also mediated through activation of PL-PFC circuits (Li et al., 2021a). Both of these studies show that ketamine's reduction of aversive pain symptoms was due, in part, by inhibition of NMDA receptors and activation of translation regulator mammalian target of rapamycin complex 1 in both ACC-PFC and PL-PFC (Zhou et al., 2018b; Li et al., 2021a). In addition, recent work shows that administration of a selective dopamine receptor 1 (D1R) agonist into the ACC-PFC restores activation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels thereby normalizing neuronal activity and attenuating both sensory and affective pain behaviors in injured rats (Lancon et al., 2021). This is consistent with previous findings reporting that agonists for serotonin receptor type 7 (5-HT7R) restores HCN channel function in the ACC-PFC and alleviates neuropathic pain in mice with chronic constriction injury of the sciatic nerve (Santello and Nevian, 2015; Santello et al., 2017). Altogether, this highlights a number of promising pharmacological interventions for recovering normal PFC activity with the goal of treating ongoing acute and chronic pain.

Nonpharmacological Interventions

Major limitations to pharmacologically resolving PFC dysfunction in pain remain 1) nonspecific targeting of drugs to areas in the central nervous system and throughout the body other than the PFC, which can create unwanted side effects, and 2) insufficient drug penetration into the brain due to the tight junctions of the blood–brain barrier (BBB). However, novel strategies for invasive and noninvasive brain stimulation are emerging that could be used to specifically manipulate PFC activity as a means to treat pain and pain-associated comorbidities.

Invasive Brain Stimulation. Although stimulation of the spinal cord has demonstrated effectiveness in treating chronic pain disorders like failed back surgery syndrome or complex regional pain syndrome, peripheral stimulation approaches like transcutaneous electrical nerve stimulation or electro-acupuncture have shown positive effects in painful diabetic neuropathy and post-herpetic neuralgia (Cruccu et al., 2007; Farrell et al., 2018). Invasive neurostimulation of (prefrontal) cortical and subcortical regions has primarily focused on motor cortex stimulation and deep brain stimulation (DBS) of diverse thalamic nuclei, periaqueductal, or periventricular gray matter, with conflicting evidence regarding efficacy to treat chronic pain (Farrell et al., 2018; Frizon et al., 2020; Knotkova et al., 2021). Recently, the ACC-PFC has been proposed as a promising target for DBS, following reports that neurosurgical lesioning of this region resulted in alleviation of pain (Farrell et al., 2018). First studies applying DBS to the

ACC-PFC of neuropathic pain patients reported significant decreases in pain scale ratings as well as improvements in the affective components of pain (Spooner et al., 2007; Boccard et al., 2014, 2017; Pagano et al., 2023). Recent innovative preclinical work implemented a closed-loop neural feedback paradigm by which optogenetic activation or electrical DBS of PL-PFC in response to pain-induced local field potentials within somatosensory cortex (S1) or ACC significantly reduced acute and chronic inflammatory pain in rodents (Sun et al., 2022).

Noninvasive Brain Stimulation. One of the major drawbacks of techniques like DBS is their invasive nature, requiring surgical procedures for electrode implantation. In light of this, there has been a notable surge in the development of noninvasive brain stimulation techniques over the recent decades. These include different approaches designed to directly modulate neuronal activity based on distinct physical characteristics (Chang et al., 2022). One of the most extensively investigated noninvasive techniques is repetitive transcranial magnetic stimulation (rTMS) (O'Connell et al., 2018). rTMS employs an electromagnetic coil to generate a magnetic field, which alters the excitability of neurons both locally in the stimulated areas and at the innervation targets (Yang and Chang, 2020). Although high-frequency stimulation has been demonstrated to enhance neuronal excitability, low-frequency stimulation reduces it, thereby mimicking long-term potentiation and depression-like synaptic changes (Hoogendam et al., 2010; Xiong et al., 2022). Interestingly, research in healthy subjects has provided results that rTMS to the DLPFC can alter tolerance to experimental pain models (Mylius et al., 2012). Based on these findings, rTMS over the DLPFC has successfully and significantly decreased chronic pain symptoms in patients with traumatic spinal cord injury (Nardone et al., 2017) and chronic tension-type headache (Mattoo et al., 2019). The efficacy of rTMS applied to the DLPFC for the treatment of fibromyalgia and neuropathic pain patients remains inconclusive, in part due to substantial heterogeneity in study design (O'Connell et al., 2018; Knotkova et al., 2021). However, recent findings in a rat model of chronic constriction injury have shown that rTMS not only reversed mechanical allodynia and thermal hyperalgesia, but also induced alterations in the expression levels of brain-derived neurotrophic factor, tumor necrosis factor-α and interleukin-10 in the PFC, potentially exerting anti-inflammatory effects (Toledo et al., 2021). There is also innovative work showing that intravenously injected magnetoelectric nanoparticles can reliably evoke cortical activity in mice using a low intensity magnetic field (Nguyen et al., 2021). It has been reported that magnetoelectric nanoparticles have limited toxicity (Kaushik et al., 2016) making them an attractive candidate for use in restoring activity in specific regions and/or neuronal populations within the PFC of pain patients.

Transcranial direct current stimulation (tDCS) makes use of weak electrical currents that are applied to specific brain regions via two or more electrodes on the scalp, thereby resulting in increased or decreased excitability depending on the polarity of the electrodes used (i.e., anodal tDCS and kathodal tDCS, respectively) (Pacheco-Barrios et al., 2020). Although the majority of studies investigating the effects of tDCS on chronic pain conditions, including fibromyalgia and neuropathic pain, target the primary motor cortex (M1) due to its connection to other pain-associated brain structures (e.g., cingulate gyrus, prefrontal cortex, and insula), individual studies targeting the DLPFC revealed increases in pain thresholds and pain perception in healthy subjects (Boggio et al., 2008, 2009b) and reduction of pain scores in fibromyalgia and knee osteoarthritis patients in home-based settings (Brietzke et al., 2020; Martorella et al., 2022). Similar results have been generated in a recent preclinical study showing that tDCS of the PFC alleviates pain and aversive behaviors in neuropathic pain mice (Gan et al., 2021), which is consistent with reported pain-relief observed in tDCS of PFC in humans (Lefaucheur et al., 2008). In patients undergoing total knee arthroplasty, tDCS of PFC, but not M1, reduced opioid use in the 3-day period following surgery (Borckardt et al., 2017), which strengthens the clinical relevance of PFC stimulation as an adjunctive therapy for pharmacological treatment of surgical pain. However, discrepancies over the effectiveness of tDCS remain as systematic reviews and meta-analysis report limited evidence for a pain reducing effect of tDCS targeted to the PFC in fibromyalgia or neuropathic pain (Zhu et al., 2017; Knotkova et al., 2021; Wen et al., 2022), which means improvements are needed in this area.

Nevertheless, tDCS is reported to be safe, easy, and well-tolerated in humans (Boggio et al., 2006, 2009a; Bikson et al., 2016) making it a promising technique for new therapeutic avenues. One example involves targeted drug delivery to specific brain regions by utilizing the effects of tDCS on enhancing BBB permeability, which has been shown in the rat (Shin et al., 2020). Compounds designed to manipulate specific PFC cellular or circuit activity could be focally delivered by increasing permeability of the BBB over the PFC using tDCS. This method would restrict the site of drug delivery to the PFC, which should reduce risk of unwanted side effects and widen therapeutic indexes. The tDCS increase BBB permeability is also reversible in the rat (Shin et al., 2020). Based on our recent findings showing that SNI and surgical pain induce hyperactivity of PL-PFC-Dyn+ neurons (Zhou et al., 2023), therapeutics aimed at reducing PFC-Dyn+ circuit activity or antagonizing Dyn neurotransmission originating from PFC-Dyn+ neurons could be focally delivered by increasing permeability of the BBB over the PFC in humans using tDCS. Using this novel principle, even the use of site-specific viral gene-therapy or nanoparticle delivery could be accomplished. Nonetheless, further development is needed in using tDCS for focal drug delivery in the human brain as data from the rat were shallowly limited to within 100–200 μm of the pia mater (Shin et al., 2020), and the efficacy and safety of repeatedly using this method remains unclear.

Along with tDCS, transcranial laser stimulation (TLS) has been clinically used for treating deficits caused by brain injury and stroke (Hummel et al., 2005; Miniussi et al., 2008; Demirtas-Tatlidede et al., 2012). The use of TLS is based on the absorption of photon energy by cytochrome oxidase, the terminal enzyme of mitochondrial respiration, and thereby stimulating ATP production and enhancing neuronal capacity for metabolic energy production (Gonzalez-Lima and Barrett, 2014). Although in healthy volunteers beneficial effects have been found for cognitive and emotional functions (Gonzalez-Lima and Barrett, 2014), application in stroke patients did demonstrate the safety of TLS and improved outcome of acute stroke when initiated within 24 hours of stroke onset (Zivin et al., 2009). TLS has also been shown to enhance BBB permeability (Li et al., 2021b, 2023) and could therefore be used for target-specific delivery of compounds to the PFC.

Last, transcranial focused ultrasound (tFUS) is a novel technique that depends on mechanical interaction of ultrasound

waves with neuronal membranes, which affects membrane permeability and ion channel gating properties (di Biase et al., 2019). As compared with the other noninvasive brain stimulation techniques, it offers increased penetration depth and smaller focus, thereby offering an unprecedented possibility to target brain regions inaccessible to rTMS or tDCS (Badran and Peng, 2024). In healthy volunteers, tFUS of the anterior thalamus attenuates thermal pain sensitivity (Badran et al., 2020) and stimulation of the primary somatosensory cortex S1 significantly attenuated somatosensory evoked potentials and enhanced performance on sensory discrimination tasks (Legon et al., 2014). Stimulation of the posterior frontal cortex via tFUS improved mood and pain scores in chronic pain patients; although this effect was only investigated 40 minutes poststimulation (Hameroff et al., 2013). Interestingly it has been shown in mice that by fine-tuning the tFUS pulse repetition frequency, specific excitatory and inhibitory neuron types could be selectively targeted (Yu et al., 2021). This highlights the potential use of tFUS for stimulation of diverse subpopulations of neurons in the PFC, which would be a key therapeutic advancement given the extensive evidence of cell- and circuit-specific changes within the PFC in preclinical pain studies (Metz et al., 2009; Lee et al., 2015; Zhang et al., 2015; Kelly et al., 2016; Radzicki et al., 2017; Cheriyan and Sheets, 2018; Huang et al., 2019; Mitric et al., 2019; Jones and Sheets, 2020; Zhou et al., 2023). In addition, clinical trials exploring the use of tFUS to temporarily opening the BBB to improve delivery of pharmacological compounds to brain tumors are ongoing (ClinicalTrials.gov identifier: NCT05762419) and could be used as a template for targeting PFC circuits in pain patients.

Here, we summarize years of research describing the involvement of the PFC in modulating both sensory and affective dimensions of acute and chronic pain in rodents and humans. This supports the growing need to progressively develop pharmacological and noninvasive neuromodulation techniques directed at the PFC, or even a combination of both, that could cultivate new possibilities of personalized or patient-specific therapies for improving treatment of different pain disorders. One promising example mentioned is this review is PFC stimulation as adjunctive therapy for surgical pain (Borckardt et al., 2017), which could be improved or adjusted for sex and inter-individual variability. Nevertheless, the only recommendation for neuromodulation of the PFC included in evidence-based guidelines is a level B recommendation (probable efficacy) for high-frequency rTMS of the left DLPFC in fibromyalgia (Lefaucheur et al., 2017, 2020). Although this review highlights the significant strides made in understanding the role of the PFC in pain modulation, continued research is critically needed to provide new insight into how these novel and emerging therapeutic strategies could be incorporated to safely treat different forms of pain and comorbid conditions caused by pain. This will not only help to overcome regulatory barriers but will also facilitate the adoption of these techniques into routine clinical practice, thereby enhancing accessibility and efficacy in pain management strategies.

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Wrote or contributed to the writing of the manuscript: Kummer, Sheets.

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