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REVIEW | *Translational Physiology*

Medial prefrontal cortex in neurological diseases

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Xu P, Chen A, Li Y, Xing X, Lu H. Medial prefrontal cortex in neurological diseases. *Physiol Genomics* 51: 432–442, 2019. First published August 2, 2019; doi:10.1152/physiolgenomics.00006.2019.—The medial prefrontal cortex (mPFC) is a crucial cortical region that integrates information from numerous cortical and subcortical areas and converges updated information to output structures. It plays essential roles in the cognitive process, regulation of emotion, motivation, and sociability. Dysfunction of the mPFC has been found in various neurological and psychiatric disorders, such as depression, anxiety disorders, schizophrenia, autism spectrum disorders, Alzheimer's disease, Parkinson's disease, and addiction. In the present review, we summarize the preclinical and clinical studies to illustrate the role of the mPFC in these neurological diseases.

cortical region; medial prefrontal cortex; neural circuit; neurological disease; pathophysiology

INTRODUCTION

The medial prefrontal cortex (mPFC) is a cortical region with different cell types and projections. As a control board, the mPFC integrates information from numerous input structures and converges updated information to output structures through the connections with other cortical and subcortical areas (85). It plays an essential role in many brain functions, including cognitive process, regulation of emotion, motivation, and sociability. Lesion of the mPFC, leading to the impairment of these functions, has been implicated in various neurological and psychiatric disorders, such as depression, anxiety disorders, schizophrenia, autism spectrum disorders (ASDs), Alzheimer's disease, Parkinson's disease, and addiction (31, 67, 131). Thus, accurate assessment of the alteration on structural organization and neural circuit function in the mPFC by these different neurological diseases has essential implications for understanding the pathology and developing therapeutic strategies for these diseases. As the anatomical features of the mPFC are sophisticated, multiple experimental methods, including brain lesions, pharmacological intervention, electrophysiological techniques, chemogenetic, and optogenetic approaches, have been employed in recent studies, which to some extent substantially promote the dissection of the mPFC circuitry and the revelation of its role in neurological diseases (97, 105). In the present review, we first attempt to outline briefly the anatomical features of the rodent brain mPFC, including cell types, laminar pattern, and projections with multiple brain regions. Then, we review the preclinical and clinical studies to illustrate the role of the mPFC in several specific neurological diseases.

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ANATOMY

Laminar Organization

According to anatomical, electrophysiological, and computational studies, the rodent mPFC seems to combine elements of anterior cingulate cortex (ACC) and dorsolateral PFC (dlPFC) from the primate at a fundamental level (111). Based on cytoarchitectural differences, the rodent mPFC is classified into four distinct neuroanatomical subregions along the dorsal to the ventral axis: medial precentral area, ACC, prelimbic cortex (PL), and infralimbic cortex (IL) (48). Among them, ACC and dorsal region of the PL are also defined as the dorsal component (dmPFC), while the ventral PL, IL, and dorsal peduncular cortex (DPC) belong to a ventral part (vmPFC). These regions have connectional and functional homology to human Brodmann areas. Although the granular layer IV is less well defined compared with humans or nonhuman primates (70, 122), the rodent mPFC exhibits laminar organization that could be divided into six distinct layers (I–VI, Fig. 1). Layer I is the most superficial, populated with sparse neurons and abundant fibers from lower layers and proximal/distal brain areas (88). Layers II/III and layers V/VI contain pyramidal neurons whose apical dendrites dwell in layer I receiving input from multiple brain regions (86). Laminar organization patterns are inconsistent among subregions. For instance, layer V in the PL is better organized than that in the ACC, while its layers II and III appear broader than neighboring subregions, indicating a distinct information processing mechanism in these subregions of the mPFC (125).

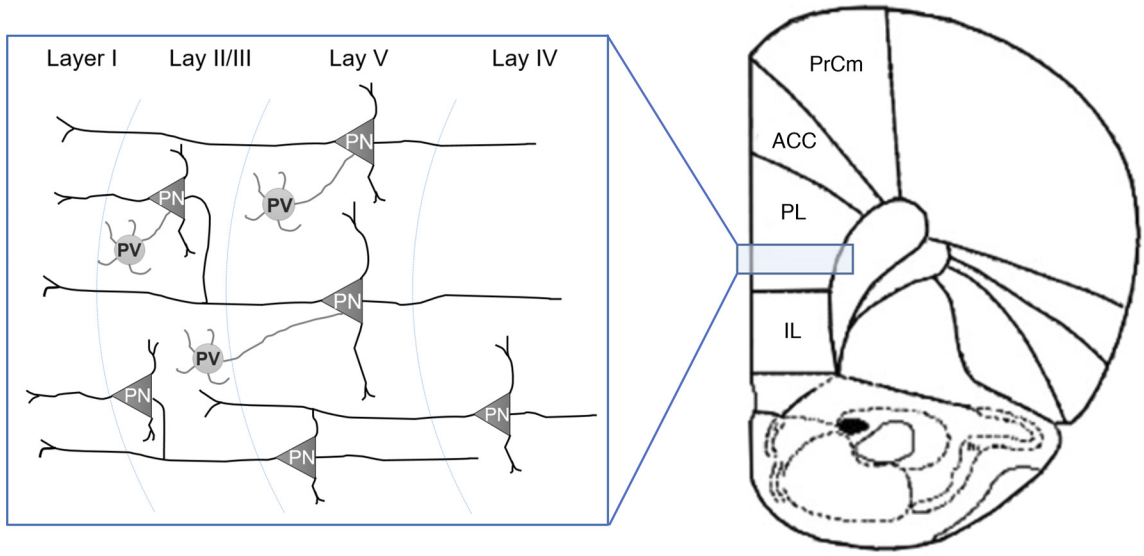

Fig. 1. Schematic structure of different regions and layers of the medial prefrontal cortex (mPFC). The mPFC consists of four distinct neuroanatomical subregions along the dorsal to ventral axis: medial precentral area (PrCm), anterior cingulate cortex (ACC), prelimbic cortex (PL), and infralimbic cortex (IL). Its laminar organization is divided into six distinct layers (I–VI) from the superficial, and the pyramidal neurons (PN) and parvalbumin (PV) interneurons in those layers maintain an excitation/inhibition balance to achieve the normal functions of the mPFC.

Cell Types

The mPFC neural network consists predominantly of excitatory pyramidal neurons (~80–90% of the total population) and inhibitory GABAergic interneurons (~10–20%). Pyramidal cells, which are mainly found in layers II-VI, show differences in cell body size, dendritic morphology, and firing properties across layers. They usually communicate with long-distance targets (27, 123). Different from pyramidal cells, interneurons serve to orchestrate cortical network dynamics. Based on their physiological and molecular properties, the interneurons could also be divided into several subpopulations, including the perisomatic targeting fast-spiking parvalbumin (PV) interneurons, the dendritic targeting somatostatin (SST) interneurons, vasoactive intestinal polypeptide (VIP), and cholecystokinin interneurons (38, 61, 62). The PV neurons, which account for over 40% of the whole interneuron population (24), are found to regulate principal glutamatergic output and theta oscillations, contributing to a particular clinical interest. Meanwhile, the SST neurons usually modulate the input received by principal pyramidal neurons (71). The pyramidal neurons in the mPFC and specific subtypes of interneurons are cooperatively engaged in an array of behaviors.

Connectivity

The PL and IL pyramidal neurons receive functional input from regions including, but not limited to, midline thalamus, basolateral amygdala (BLA), ventral hippocampus (vHipp), and the contralateral mPFC. The projections in the laminar pattern play different roles in signal processing. Afferent projections from limbic and cortical regions mainly target the superficial layers I and II/III. Among those afferents, thalamocortical connections are vital for mediating sensation, consciousness, and perception process (43, 76, 83). The thalamus also projects to the layer I of both dmPFC and vmPFC, driving fast and robust synaptic responses of late-spiking interneurons in layer I, which provide feed-forward inhibition of layer II/III pyramidal cells (26). Studies also reported robust connectivity from the BLA to layers II–VI, and some of them projecting to interneurons, which allows BLA neurons to modulate mPFC activity through feed-forward inhibitory mechanisms (75).

The efferent fibers from the mPFC mainly project to cortical and subcortical brain regions, which enables it to have control over visceral, automatic, cognitive, and limbic functions (50). Glutamatergic projections of the mPFC to the nucleus accumbens (NAc) core and shell play a significant role in cognitive processing, including reward, aversion, motivation, and reinforcement. Besides, there is evidence for the existence of the projections from the mPFC GABAergic neurons to the NAc (72), indicating that not all GABAergic interneurons in the mPFC are strict local neurons. The PL projection to the BLA is another important connection that integrates higher cognitive processing with innate emotional responses (137). The BLA-projecting PL neurons, which mainly dwell in layer II and target the pyramidal neurons and partial interneurons in the BLA, mediate the feed-forward inhibition of GABAergic transmission in some cases (52). Given that BLA inputs also target the soma or dendrites of the PL neurons, this reciprocal connectivity between them might enable efficient bidirectional communication, contributing to precise control on emotion.

Reciprocal cortico-cortical interactions within the mPFC mainly originate from layer II and III. Compared with the PL, the IL neurons exhibit higher frequency in local field potential components, which further differ when the two regions are disconnected (124). Furthermore, increasing activity of the deep layer IL neuron in vivo via photostimulation reduces both spontaneous and evoked synaptic activities of PL pyramidal cells via feed-forward inhibition mechanism (55). This indicates that IL-mediated behavior may involve suppressing PL function, such as fear extinction.

MPFC AND NEUROLOGICAL DISEASES

Depression

Depression represents the second-leading cause of mental disability worldwide and has drawn concerted research effort. It is characterized by a series of symptoms (behavioral, cognitive, affective, and somatic) and high recurrence risk. The mPFC is one of the critical brain regions involved in the pathogenesis of depressive symptoms. It plays a crucial role in the affective and cognitive deficits in depression. We review the main factors in the mPFC that contribute to depression.

The altered morphology and neuronal activity in the mPFC are closely related to depression. Decreased basilar and apical dendritic branching of the mPFC neurons has been found in mice experiencing corticosterone or stress exposure or tumor burden (29, 90, 100). Meanwhile, shifted mPFC activity and abnormal functional connections of the lateral region are observed in depression patients with self-focus through functional magnetic resonance imaging (134). In mice following chronic social defeat stress (CSDS), the reduced functional activity, indicated by the decreased expression of immediate early gene zif268 in the mPFC, is also very significant (24a). Indeed, activation of the mPFC of CSDS mice via optogenetic stimulation improves social interaction and sucrose solution preference score, without affecting general locomotor activity, anxiety-like behaviors, or social memory (25). CSDS can also cause a decline in the expression and function of Panx1 in the mPFC, a new gap junction channel in the brain mediating efflux of ATP, resulting in an energy shortage of the mPFC neurons (91). Chronic gestational stress is another factor influencing the mPFC function. It causes compromised structural plasticity in the mPFC and impaired performance of the mouse model on an attentional set-shifting task (73). Altered levels of dopamine and noradrenaline (NA) in the limbic and limbic-related brain regions are also shown to be involved in the regulation of depressive-like behaviors (138). However, mPFC function is influenced through a different mechanism in Parkinson's disease-related depression. The decreased firing rate of mPFC neurons associated with this disease-caused depression is mediated by inhibition of serotonin (5-HT)6 receptors in the PL.

The reciprocal interaction of the mPFC with other brain regions is demonstrated to be involved in the social defeat-induced depression. For instance, while increasing the phasic firing of the mPFC-projecting neurons in the ventral tegmental area (VTA), the depressive-like mice that receive subthreshold social defeat paradigm exhibit higher stress susceptibility (19). This paradigm contains 2 min of physical attack and 10 min of sensory stress (two rounds), which bring mild defeat to mice. On the contrary, archaerhodopsin-mediated photoinhibition of the vmPFC inputs to the dorsal raphe nucleus (DRN) prevents the progress of social withdrawal in animals subjected to social defeat (18). The vHipp-mPFC pathway is also involved in depression. Optogenetic or chemogenetic specific activation of the vHipp-mPFC pathway could mimic the antidepressant-like response to ketamine, while optogenetic inactivation of this pathway during a forced swim test reversed ketamine's antidepressant effect. It demonstrates that the vHipp-mPFC pathway is causally related to the antidepressant effect of ketamine (17).

Anxiety Disorders

Anxiety refers to the brain response to danger or stimuli that an organism tries to avoid actively, which is adaptive in many scenarios facilitating avoidance of danger. However, exaggerated or poorly controlled anxiety responses (anxiety disorder) can be disruptive (114). Anxiety disorders are characterized with common features, such as extensive anxiety, inhibited temperament, tendency to be shy and to avoid new situations, behavioral disturbances such as extreme avoidance of feared objects and associated impairment. It includes panic disorder, agoraphobia, and subtypes of specific phobias (5). As the mPFC is highly involved in emotional control, it has been implicated in understanding and modulating anxiety.

Alterations of neuron activity, synaptic plasticity (21), and connectivity within the mPFC (22) are correlated with high risk for anxiety disorders, especially for children with early-life stress (ELS). Treatment with high-frequency repetitive transcranial magnetic stimulation in the mPFC could significantly reduce anxiety and avoidance ratings in patients with anxiety disorders (49). In Wistar-Kyoto rats with impaired extinction of avoidance behavior, paired housing facilitates the extinction of lever-press avoidance, accompanied by altered neuronal activity in the mPFC, indicating the association of the mPFC with avoidance behavior (116). On the other hand, mPFC lesions induce anxiety-like behavior. Bilateral focal ischemic lesions restricted to the mPFC could mimic poststroke anxiety in rats (28), demonstrating a key role of the PL subregion in anxiety.

Multiple neurotransmitter systems of the mPFC, such as glutamatergic, GABAergic, cholinergic, and serotoninergic systems, contribute to the pathophysiology of anxiety disorders. NMDA receptor-mediated glutamatergic neurotransmission mediates the anxiogenesis of the sodium channel activator veratrine. Veratrine could increase the time in the center zone of the open field by elevating PL extracellular glutamate levels. Coperfusion of an NMDA receptor antagonist, MK-801, or Riluzole, which directly affects the glutamatergic system, diminished increased anxiety in open field tests with or without attenuating veratrine-induced elevated extracellular glutamate levels (92, 109). A significant decrease in GABA was detected in the ACC and mPFC in panic disorder patients (78). Infusion of $GABA_A$ receptor antagonist bicuculline temporarily activated the IL cortex, which decreased the anxiety level in the open field test and elevated plus maze (EPM) test, accompanied by smaller evoked inhibitory postsynaptic currents (IPSCs) and larger evoked excitatory postsynaptic currents (EPSCs) in pyramidal neurons. This impaired excitation/inhibition balance toward increased excitation in the IL subregion of the mPFC underlies the pathogenic mechanism of anxiety disorders (7). Interestingly, a study in mice showed that activation in the PL, but not the adjacent IL subregion in the mPFC, generates anxiety-like behaviors. The inconsistent results may be induced by different activation methods or mouse strains (120). For the cholinergic system, intra-PL administration of an acetylcholinesterase inhibitor, neostigmine, could produce an anxiogenic-like effect. It decreased the time that the animal spent in the open arm in the EPM test and increased its time in the dark chamber in light-dark box test. However, the previous injection of pirenzepine (M1 receptor antagonist) abolished this response in the EPM test (35). Meanwhile, suppressing the

muscarinic receptor (atropine, J104129 fumarate or pirenzepine) in ventral mPFC attenuated the expression of the conditioned emotional response of rats during re-exposure to the aversive context. It indicates that the GABAergic system in mPFC is involved in the control of anxiety-like behaviors (33). 5-HT-mediated neurotransmission also contributes to the anxiogenic effects of drugs, such as cannabidiol, which could decrease the open arm exploration of rats in EPM by facilitating 5HT1A receptor-mediated neurotransmission (36). More direct evidence showed that 5HT(1A) or 5HT(1B) receptor agonist administration in bilateral intra-mPFC induces anxiogenic response in rats, while the administration of 5HT(1A) receptor antagonist could reduce anxiety (117). Recent studies reported that the other 5-HT receptors, including 5-HT4, 5-HT6, 5-HT7, in mPFC also show different roles in the anxiety state (30, 32, 39).

Besides the above neurotransmission system, some other modulatory systems are also involved in regulating anxiety level. For example, neuronal nitric oxide synthase (nNOS)-mediated signaling in the mPFC is shown to mediate the anxiogenic-like effect induced by restraint stress (126) or predator exposure, reflected by increased nNOS expression or NOx levels (15). Exogenous oxytocin application to the mPFC can attenuate anxiety-related behavior (108). It may engage GABAergic neurons to modulate downstream brain regions associated with anxiety (107).

The altered connectivity between the mPFC, vHipp, or BLA contributes to the changes in anxiety status. The projection from the vHipp to the mPFC exhibits anxiety-related neural synchrony in a pathway-, frequency-, and task-specific manner, by which the hippocampus conveys information to the downstream structures (2, 94). This synchronized process of anxiety regulation is attributed to the neuronal gap junctions between the vHipp and mPFC, leading to the generation of highly temporally correlated firing activities (110). Meanwhile, the vHIP-mPFC pathway also underlies the spatial representations of aversion (94). In addition to this pathway, anxiety-like behavior induced by the mPFC stimulation may be partially mediated by activation of the amygdala (135). For example, increased mPFC-BLA synchrony in the theta frequency range is only observed in animals that can differentiate between aversion and safety. This selective tuning of BLA firing following mPFC input provides a safety-signaling mechanism to overcome anxiety or fear (74).

The density and morphology of dendrites in the mPFC pyramidal neurons are closely related to anxiety-like behavior of animals. Anxious rats have smaller apical dendrites in layer II/III of the PL compared with normal rats (87). Thus, how likely ELS will cause anxiety disorders could be predicted by the density and morphology of spines in the apical dendrites of mPFC pyramidal neurons (119).

Schizophrenia

Schizophrenia is a systemic psychiatric disease characterized by delusions, hallucinations, loss of initiative, and cognitive dysfunction. The cognitive deficits, such as impaired episodic and working memory and compromised affective control, were found to be due to dysregulated PFC function and altered connectivity with subcortical regions (4).

Altered dopaminergic modulation in the mPFC is involved in schizophrenia progression. The blunted release of dopamine in the PFC is a hallmark of schizophrenia pathophysiology. Dramatically reduced dopamine release in the mPFC was observed in many clinical patients and mice with hypofunctional GABAergic neuron-specific N-methyl-D-aspartate receptors (NMDARs) (89). Among dopaminergic pathways, D2-receptor (D2R) trafficking regulated by Dysbindin-1 in the mPFC is involved in schizophrenia (95). Impaired enhancement of the excitability of L5 pyramidal neurons in the mPFC by D2R activation through a pathway associated with Gs, rather than Gi/o as classically reported, may contribute to the prefrontal dysfunction in schizophrenia (106). Dopamine transporter deletion causes a decrease in spine density of mPFC pyramidal neurons, leading to hypofunction of the mPFC, which may contribute to the schizophrenia-relevant behavioral abnormalities, such as hyperlocomotion, cognitive deficits, impulsivity, and impaired prepulse inhibition of the startle reflex (60). Decreased dendritic spine density of pyramidal neurons in the mPFC is also present in postmortem studies or schizophrenia models induced by neonatal BLA lesion (41, 118).

Decreased GABAergic signaling is dominant in the pathology of schizophrenia. Evidence shows that the reduced density of PV or SST interneurons in the mPFC occurs in numerous models of schizophrenia, including methylazoxymethanol acetate-treated mouse (77), the *Plaur* null mouse (8), *BRINP1*-knockout (KO) mouse (69), and "double hit" model developed using the Lister Hooded rat subjected to MK-801 injection at postnatal *day 7* and socially isolated from postweaning to adulthood (40). However, increasing the number of PV-expressing cells in the mPFC via endogenous HGF/SF overexpression could not halt the behavioral deficits in the *Plaur* null mouse (8). Thus, loss of interneuron function in the mPFC might be the consequence, rather than the causal factor, for impaired cognition in schizophrenia.

Altered connectivity between the mPFC and other brain regions is also involved in schizophrenia. The decrease in the connectivity between mediodorsal thalamus (MD) and the mPFC may mediate the impaired working memory observed in schizophrenia patients, given that the projections of MD-to-mPFC and mPFC-to-MD support working memory maintenance and subsequent choice, respectively (9). Abnormal inputs from the BLA and the vHipp to the mPFC during postnatal development might also underlie the pathophysiology of schizophrenia (6).

Autism Spectrum Disorders

ASDs are a heterogeneous, early-onset group of heritable neuropsychiatric diseases. A combination of genetic, epigenetic, and environmental factors is thought to induce multiple ASD symptoms, including deficits in social interaction and communication abilities, and ritualistic-like repetitive behaviors (66). The PFC and its projections have been widely implicated in ASDs to explain the deficits related to sociability, emotion, cognition, and language.

Alteration of the balance between neuronal excitation and inhibition (E/I balance) in the mPFC is involved in autism-related phenotypes. It mainly results from the changes in the number, functional activity, or morphology of GABAergic

interneurons. A decreased number of PV interneurons is also found in postmortem neocortical tissue (46) and many ASDs models, such as *PV*$^{+/-}$, *Shank1*$^{-/-}$, and *Shank3B*$^{-/-}$ mice (34) and neonatal phencyclidine-treated rats (57). This "reduction of PV interneurons" may be due to the reduction in PV mRNA and protein level, or the mitochondrial dysfunction that induces energy deficit, rather than neuronal cell death (34, 54). Decreased excitability of fast-spiking interneurons and dysfunction of gamma oscillation in the mPFC are found in *CNTNAP2* KO mice (113) and *NL3 R451C* knock-in mice (16). Optogenetic or pharmacological stimulation of PV neurons or inhibition of pyramidal neurons in the mPFC could ameliorate deficits in social interaction, hyperactivity, and cognitive performance in many mouse models (16, 81, 113), indicating the causal role of the dysfunction of the mPFC GABAergic signaling in the pathogenesis of social and cognitive deficits of ASDs. Along with the neuronal alterations, neuroinflammation in the mPFC is also considered to contribute to ASD pathophysiology. Increased levels of tomato lectin, glial fibrillary acidic protein, and adhesion molecule (NCAM) in the mPFC occur in valproic acid (VPA)-treated animals (23).

Among projections related to the mPFC, the specific deep-layer prefrontal neurons that project to subcortical targets, such as MD, are closely associated with social behavior. The L5 subcortically projecting neurons exhibit reduced input resistance and action potential firing across three distinct models, including in utero VPA exposure, *CNTNAP2*-KO, and *FMR1*-KO mice (14). Although the hypofunctionality of the mPFC in autism is a prevalent mechanism for ASDs as we described above, the hyperconnectivity and hyperplasticity in the mPFC are also found to be related with some autistic symptoms, such as impaired sociability, repetitive multitasking behaviors, and attention deficit. The hyperconnectivity and slow synaptic transmission during early development of the mPFC were observed in *FMR1*-KO mice, a mouse model for autism and mental retardation (121). Furthermore, the axonal projections from mPFC to BLA show increased axonal branching and connectivity, which lead to increased activity in the BLA of *Pten*$^{+/-}$ mice, a model for autism and macrocephaly (51).

Alzheimer's Disease

Alzheimer's disease (AD), a neurodegenerative disorder, is the most common form of senile dementia. It is characterized by extracellular amyloid β peptide (Aβ) plaque deposition and intracellular neurofibrillary tangle formation in the cerebral cortex, leading to severe cognitive deficits, emotional depression, and motor dysfunction gradually. AD patients typically suffer from the loss of working memory, spatial memory, and anterograde memory. The mPFC, which could generate mental representations in the absence of sensory stimulation, plays a crucial role in working memory. Accumulating evidence shows that several symptoms of AD are related to pathological or functional changes in the mPFC.

Neuronal ensemble activity and functional connectivity among neurons could effectively encode and process information input into the brain. The default-mode network (DMN) is defined by structural interconnections among the mPFC, the posterior cingulate cortex and adjacent ventral precuneus, and parietal cortex. Its functional connectivity reflects the consciousness, integrates sensory, affective information, and generates spontaneous thoughts. Functional connectivity in the DMN and the ability to suspend DMN activity both decline during aging and in the patients with mild AD (115). Additionally, Aβ injection of rats leads to poor behavioral performance and the lack of experience-induced increase of neuronal activity and connectivity in the mPFC during working memory tasks, indicating a circuit-level mechanism underlying Aβ-induced working memory deficits (132). However, constant cortical activity in the mPFC could accelerate AD progression. It promotes activity-dependent Aβ accumulation, accompanied by the breakdown of the vHipp-mPFC interplay across sleep stages, which contributes to memory consolidation deficit (59). Evidence obtained from primates shows that AD is associated with changes in the synapses on the spines containing NMDARs specifically with NR2B subunits (GluN2B) in the dlPFC (128).

Memory deficit in AD can also be attributed to the modification on dendritic spine density and morphology in the mPFC and the hippocampus. Dendritic spine density usually increases following the consolidation of initial memories, contributing to a type of continued plasticity to store long-term memories. In the ovariectomized (OVX) animal model of AD, dendritic spine density was decreased 17–53% in the mPFC and hippocampal CA1 region, followed by the decline of memory performance 7 wk post-OVX (127). Recently, Rho-associated protein kinase isoform 1 has been shown to be an attractive drug target for AD as it regulates mPFC neuronal dendritic structure (42).

Oxidative stress is another important factor in AD progress. The neuronal loss in the mPFC and poor cognitive performance was observed in the rats administered with intracerebroventricular colchicine, a microtubule-disrupting agent known to cause oxidative stress. Thus, the antioxidant supplement is likely to prevent neuronal loss by reducing tau accumulation during the progression of AD (56).

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disease that is characterized by motor symptoms, including rigidity, postural instability, resting tremor, bradykinesia, and nonmotor features, such as emotional and cognitive deficits. As a critical part of the cortex–limbic–striatal pathway, the mPFC and its connected regions have been found to be associated with the pathophysiology of nonmotor symptoms in PD (101).

Dopaminergic degeneration not only is a key factor of motor dysfunction in PD but also contributes to the cognitive deficits of PD (58). One key dopamine signaling pathway projects from the VTA to the marginal region and then to the frontal cortex, forming the cortical pathway (3). Both PD patients and mice with VTA dopamine depletion showed impaired behavioral performance and attenuated delta activity in the mPFC during interval timing, a task that requires participants to estimate an interval of several seconds as guided by a cue and requires executive resources such as working memory and attention to time (96). Optogenetic stimulation of the mPFC neurons expressing dopamine receptor D1 at delta frequencies can reduce the deficits in temporal control of action caused by VTA dopamine depletion (65). The mouse model with 6-hydroxydopamine (6-OHDA)-induced lesion in the medial fore-

brain successfully recapitulates multiple phenotypes of PD (80). Bilateral dorsolateral striatum injection of 6-OHDA causes decreased monoamine levels in the striatum and PFC, accompanied by motor deficits. Notably, reduced monoamine levels and selectively decreased amplitude of long-term potentiation in the mPFC also occur in 6-OHDA-lesioned rats, which exhibit short-term memory deficits. Thus, the short-term memory dysfunction in PD is associated with malfunction of the mPFC circuits (82).

Serotonergic pathways also play an essential role in regulating mPFC function. Several subtypes of 5-HT receptors are expressed in the mPFC, including 5-HT(1A) and 5-HT(2A) subtypes (30a). The serotonergic system is found to be affected by PD progression. Lesion of the substantia nigra pars compacta induces hyperactivity of mPFC pyramidal neurons and abnormal firing pattern in response to 5-HT(1A) receptor stimulation (129). It also decreases the firing rate of fast-spiking interneurons; the firing pattern becomes more burst-firing in both slow-spiking and fast-spiking interneurons in the mPFC (44).

The noradrenergic neurotransmitter system in the locus coeruleus (LC) also participates in the pathogenesis of nonmotor symptoms in PD, such as depression and dementia. Neuroimaging and postmortem studies have found significant noradrenergic neuron loss in the LC and NA depletion in the cortex of PD patients with depression and dementia (10, 101, 139). Moreover, lesions in the LC could lead to hyperactivity of the mPFC pyramidal neurons of rats, which is likely to be partially mediated by the postsynaptic alpha (2)-adrenoceptors on these neurons (130).

The mPFC closely interacts with the subthalamic nucleus (STN), a promising therapeutic target for PD as it is a critical site for motor control. Neuronal activity in the STN is found to be synchronized with 4-Hz oscillations in the mPFC during cognitive processing. In fact, low-frequency (4 Hz) deep brain stimulation (DBS) in the STN could be an effective treatment for PD as it improves both motor function and cognitive performance (63).

Addiction

Addiction is a brain disorder characterized by a repeated compulsive behavior pattern engaged in drug seeking, consumption, and relapse despite severe, disadvantageous consequences (53). Drug addiction results from a series of transitions from initial, hedonic drug use to habitual compulsive use, and the relapse rate is very high for addicts are vulnerable to memories related to drug effects and environmental cues. Those processes accompany the adaptations of many neural circuits. The mPFC plays a significant role in addictive behavior. A small subset of the ventral mPFC neurons could form neuronal ensembles to encode the coupling between the reward of drug use and the associated contexts. This ensemble can be reactivated by drug-associated contexts during abstinence (11).

Repeated cocaine use could cause functional activity alterations in the mPFC (13). Glutamatergic dysfunction in the mPFC is considered as one of the mechanisms underlying the behavioral effects of compulsive drug-seeking (98). The mPFC glutamatergic output to subcortical brain regions is enhanced by the repeated cocaine exposure, partly due to the loss of inhibitory control and the reduction in cortical group II metabotropic glutamate receptors (133). The cocaine-seeking tendency may be attributed to increased neuron excitability and E/I ratio in the mPFC as 2 wk cocaine withdrawal results in increased scores in cocaine-conditioned place preference, decreased amplitude of GABAergic IPSCs, downregulated gephyrin level, and increased ratio of EPSCs/IPSCs (E/I) in the rat mPFC neurons (136). Chronic ethanol exposure can also induce hyperexcitability in the mPFC and ventral bed nucleus of the stria terminalis and a shift toward excitation in the synaptic drive (99). Cortical hyperresponsiveness enhances the susceptibility to cocaine relapse and craving, which is associated with excessive upregulation on the activity and density of high voltage-activated L-type Ca^{2+} channels (37). On the other hand, hypofunction of the mPFC is also related to drug taking or relapse. Long-term cocaine self-administration reduced PL neuron excitability, especially in aversion-resistant rats. Optogenetically restoring the function of these PL neurons alleviates cocaine intake of these rats (20), indicating that hypoactivity of PL pyramidal cells contributes to a loss of inhibitory control over compulsive cocaine intake. Moreover, decreased mPFC activity is detected in relapsing individuals with worse goal-directed control over alcohol consumption during abstinence (112).

Synaptic structure and plasticity changes in the mPFC pyramidal neurons underlie the impaired cognition induced by addiction. Chronical exposure to the synthetic cannabinoid agonist CP55,940 in adolescent rats leads to later long-lasting deficits in both short-term working and visual memories in adulthood. It may impede the structural maturation of neuronal circuits in the mPFC, given the significantly altered dendritic arborization of layer II/III mPFC pyramidal neurons, impaired vHipp-mPFC synaptic plasticity, and the changed expression of PSD95 (104). In addition, 10 wk of ethanol consumption increases total spine densities and the frequency of spontaneous postsynaptic excitatory currents in the mPFC layer V pyramidal neurons (68). However, the spine density and dendritic complexity of the mPFC Layer II/III neuron are decreased by developmental alcohol exposure (45). High levels of alcohol exposure also lead to decreased frontal lobe brain size of rodent neonates (45). The rats abstaining from cocaine self-administration also exhibit reduced dendritic branching and synaptic density in the mPFC (103). Increased expression of brain-derived neurotrophic factor (BDNF) in the mPFC is found to mediate the neuroadaptation that blunts the reinforcing efficacy of cocaine. During cocaine withdrawal, elevated BDNF enhances synaptic plasticity by suppressing GABAergic inhibition in the mPFC through the BDNF-TrkB-phosphatase 2A signaling pathway, which may contribute to cue-induced cocaine craving or seeking behaviors (79).

The connections between mPFC subregions and subcortical regions are involved in compulsive drug-taking or -seeking behavior. The mPFC and the NAc are both integral components of the corticobasal ganglia-thalamic circuitry. Studies with pharmacological and optogenetic approaches reveal the critical role of the dmPFC-NAc core and vmPFC-NAc shell pathway in drug- and cue-induced cocaine or heroin seeking (12, 84). Thus, dampening cortical control over the NAc during drug exposure may lead to long-term suppression on the probability of drugs and their related stimuli to trigger drug-seeking behavior (64). Furthermore, in a computational model, LC-originating NA in the PL and IL subregions of the mPFC

amplifies inputs into these regions, allowing them to regulate the learning processes in the amygdala. Indeed, depletion of NA from PL or IL with amphetamine impairs alcohol extinction (93).

DISCUSSION

Despite differences in symptoms and pathophysiology among distinct neurological diseases we covered above, dysfunction of the mPFC leads to several shared neurological symptoms of these diseases, including cognitive deficits, loss of sociability, and dysregulation of emotion and motivation. For example, decreased performances in learning widely affect AD patients and cocaine addicts. They both are related to impaired synaptic plasticity of the vHipp-mPFC circuit, a classical pathway mediating learning and memory. Cognitive disorders in schizophrenia and AD are associated with functional alteration in glutamatergic synapses containing NMDARs in the mPFC (128). Individuals with autism or schizophrenia show a similar decrease in sociability, which can be explained by alterations of E/I balance in the mPFC. In fact, because of the shared mPFC mechanism in some of these neurological diseases, two diseases could coexist. For instance, depression is common in AD and PD patients. This indicates the important role of the mPFC in brain function and the foundation of a connection between those different neurological diseases (Fig. 2).

The mPFC contains various types of neurons and several layers. Any structural or functional changes may lead to the loss of normal function, underlying some neurological diseases. The alteration of pyramidal neuron activity or the E/I balance of the mPFC is one of the most important mechanisms underlying its dysfunction. It could be detected in most diseases we mentioned above. From the morphological aspect, impaired synaptic or dendritic structure and decreased spine density are involved in decreased neuronal function. Insight into altered anatomical connectivity between the mPFC and other brain regions could give a more specific and detailed understanding of particular compromised neuronal function in neurological disorders. Dissection of neuronal circuitries related to particular behaviors is enabled by the development of many kinds of technologies. Traditional manipulation including lesions, pharmacological and electrophysiological methods, and more recently developed techniques, such as chemogenetic and optogenetic technology, have provided crucial knowledge of the involvement of mPFC circuitry in many neurological disorders.

Although we have gained a better understanding of the role of the mPFC in neurological disorders, the most urgent issue to address is to develop effective treatments for these diseases. Considering that the mPFC participates in numerous brain functions, one treatment targeting the mPFC might achieve

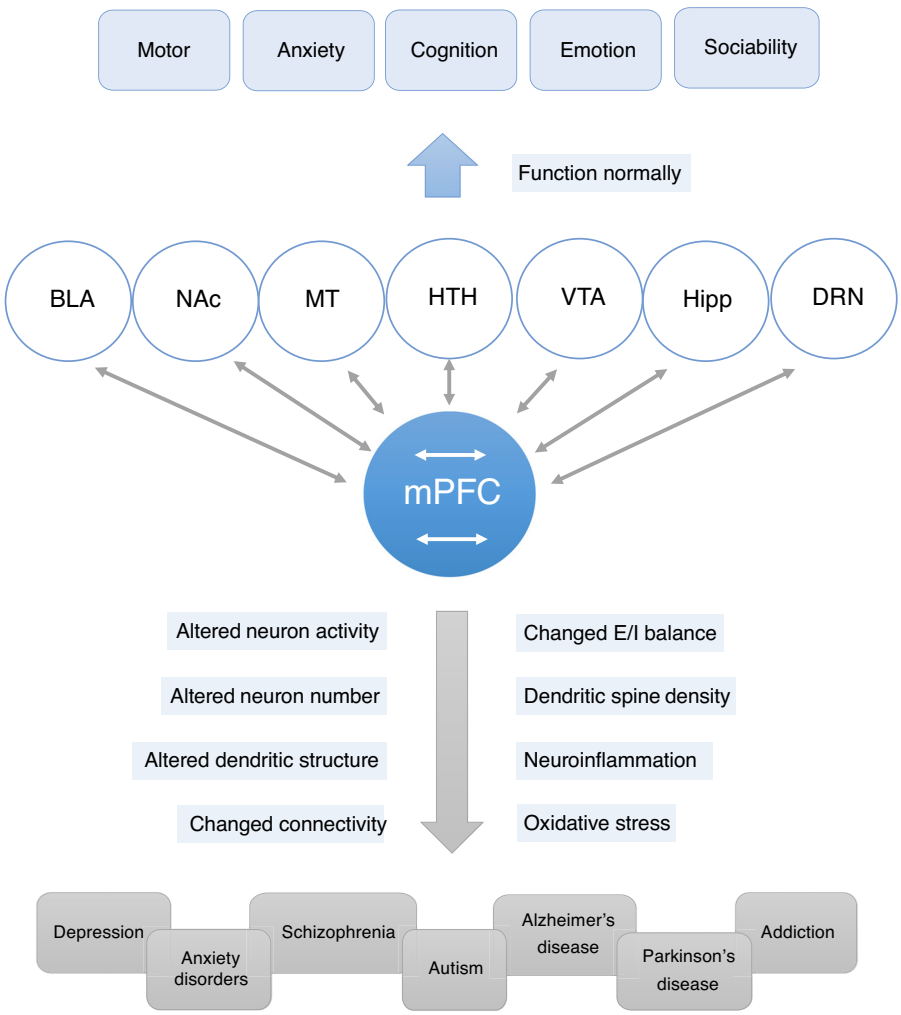

Fig. 2. The mPFC conceived as a network. The mPFC network consists of the connections within mPFC neurons and the efferents and afferents connected with the cortical or subcortical brain regions, including BLA, Nac, MT, HTH, VTA, Hipp, and DRN et al. Under normal conditions, the network shows an adaptive response to input, which allows for normal behavioral functions such as emotion regulation, cognitive flexibility, working memory, social interaction, and motor coordination. However, in pathological conditions, altered neuron activity, neuron number, excitation-inhibition (E/I) balance, connectivity or other kinds of factors in mPFC are likely to underlie multiple types of neurological disorders, like the depression, schizophrenia, autism, Alzheimer's, Parkinson's, pain and addiction. Abbreviations: mPFC, medial prefrontal cortex; BLA, basolateral amygdala; Nac, nucleus accumbens; MT, midline thalamus; HTH, hypothalamus; VTA, ventral tegmental area; Hipp, hippocampus; DRN, dorsal raphe nucleus.

improvement in multiple symptoms or diseases. However, on the other hand, the complicated structure within the mPFC and its sophisticated interaction with other brain regions create many challenges to this task. It is key to consider how to limit the treatment effect to the intended symptoms without inducing side-effects. Hence, more efforts should be taken to unveil more detailed circuit mechanisms of these diseases to provide more refined targets for DBS or pharmaceutical treatments.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

P.X. collected references, interpreted previous researches, design structure, prepared figures, and drafted manuscript; A. C., Y. L. and X. X. collected references, interpreted and summarized the previous clinical studies; H.L. edited, revised manuscript and approved the final version of the manuscript.

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