Medial Prefrontal Cortex Circuits and Their Roles in Cognition and Emotion

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Accumulating evidence has shown the importance of brain circuits in understanding cognitive and behavioral changes. For example, the medial prefrontal cortex (mPFC) plays a crucial role in various cognitive functions, such as attention, decision-making, emotion regulation, and spatial and working memory. Dysfunction in mPFC circuits has been associated with psychiatric disorders, including anxiety disorders, attention deficit hyperactivity disorder (ADHD), and addiction. Recent rodent studies have demonstrated how different mPFC-related circuits contribute to these cognitive processes.

This review highlights long-range circuits between the mPFC and other brain regions, such as the dorsomedial striatum (DMS), nucleus accumbens (NAc), thalamus, ventral hippocampus (vHPC), and basolateral amygdala (BLA). These pathways often function as reciprocal loops rather than simple one-way connections, allowing for more flexible control of behavior. For instance, the mPFCDMS pathway is involved in attention and behavioral inhibition, while the mPFCNAc and mPFCBLA pathways relate more to motivation and emotion.

This review summarizes the mPFC-related circuits and their cognitive functions, focusing on results from optogenetic, electrophysiological, and circuit-tracing approaches in rodent models. Given the increased focus on understanding the physiological mechanisms underlying psychiatric disorders, integrating different types of mPFC-related circuits may help inform new strategies to treat cognitive and emotional disorders. While these findings are primarily based on rodent studies and direct homology with humans is limited, they nonetheless provide valuable insights that may guide translational research and potential clinical interventions.

Introduction

The prefrontal cortex (PFC) plays a critical role in cognitive functions, including spatial and working memory, reward, decision-making, and emotion[1,2]. Growing evidence suggests that various neuropsychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), addiction, and anxiety disorders, have been associated with dysfunction of the PFC[3,4]. Understanding cortical circuits is important for uncovering the physiological mechanisms underlying psychiatric disorders[5,6,7,8]. Recent studies have examined the brain networks of the medial PFC (mPFC) by tracing its input and output neurons in rodent brains, which may give insight into understanding neural circuits[5,6,7,8]. Although comparing the PFC across species is a topic of debate[9,10], the rodent mPFC shares many similarities with the human medial agranular cingulate cortex[11].

At the same time, it is important to acknowledge species-specific differences. The organization of the medial prefrontal cortex (mPFC) differs substantially between rodents and humans. Notably, Brodmann area 10 (frontopolar cortex), which supports abstract reasoning and long-term planning, is present in humans and primates but absent in rodents[12]. Thus, while rodent mPFC shares certain features with the human medial agranular cingulate cortex, direct homology is limited[9]. Clinically, hypoactivity of the mPFC and related prefrontal regions has been observed in major depressive disorder and generalized anxiety disorder, highlighting its central role in mood regulation[13]. These translational differences emphasize the importance of cautious interpretation when extrapolating rodent findings to human psychiatric conditions.

It is crucial to consider how commonly studied rodent subregions relate to human prefrontal divisions. Current consensus emphasizes that these correspondences are functional rather than strict anatomical homologies[9]. For example, the rodent prelimbic cortex (PL) has been linked to executive control and decision-making functions similar to the human dorsal anterior cingulate cortex (dACC)/dorsomedial PFC (dmPFC), whereas the infralimbic cortex (IL) is more often compared to the human ventromedial PFC (vmPFC) with emotion regulation and fear extinction[9]. Likewise, rodent ACC shares conflict monitoring and error-detection properties with human medial/dorsal ACC[9]. However, these parallels should be considered as functional analogies rather than one-to-one homologies[9].

The rodent mPFC consists of several subdivisions, including the ACC, PL, and IL[11] (Fig. 1b). These regions progressively shift their cognitive functions along the dorsoventral axis, tran-

sitioning from decision-making and attention to motivation and emotion[11]. Furthermore, each region has distinct inputs and outputs, indicating differences in connectivity that likely contribute to their specific roles in behavior[11]. Previous studies have revealed the presence of diverse projection neuronal populations within the mPFC, enabling communication with other brain regions such as the basolateral amygdala (BLA), thalamus, and striatum (Fig. 1a)[11]. These circuits are mostly a network of reciprocal loops, rather than solely relying on one-way connections[14,15]. This allows the mPFC to continually update neural activity and effectively coordinate diverse behaviors[14,15].

mPFC-dorsomedial striatum (DMS)

The existence of a neural pathway connecting the prefrontal cortex (PFC) to the dorsomedial striatum (DMS) has been proposed as a mediator of cognitive control in behavior, encompassing proactive inhibitory control and attention[16]. Electrophysiological recordings of neuronal activity and local field potentials have provided further evidence for the functional coupling between the dorsal mPFC and DMS. These recordings have shown synchronized activity in both brain regions during delay periods when inhibitory control and attention are most crucial[17,18]. It has been proposed that mPFC projection neurons directly influence the activity of the DMS[19]. The glutamatergic input from mPFC terminals is believed to modulate the balance of activity between the direct and indirect pathways within the DMS[20,21]. This modulation may regulate the initiation and inhibition of actions, as well as the attentional state associated with upcoming behavior. A rodent study using selective chemogenetic and optogenetic approaches suggested corticostriatal neurons in inhibitory control. To be specific, when frontostriatal neurons were silenced, it led to deficits in inhibitory control, specifically manifested as an increase in premature responses. These frontostriatal neurons exhibited a predominance of persistent activation or silencing during inhibitory control, and altered timing of activity change in these neurons was associated with prematurely expressed responses in the task. Among the mPFC neuronal population, a higher proportion of frontostriatal projection neurons displayed task engagement with persistent changes in firing rate. Together, these results support the role of frontostriatal projection neurons in controlling behavioral inhibition[22].

Studies have shown that corticostriatal inputs produce distinct synaptic responses in D1- versus D2- medium spiny neurons (MSNs)[23]. Moreover, whole-brain mapping indicates that D1- and D2-MSNs differentially receive input from cortical areas, including the mPFC[24]. D1-MSNs generally promote action initiation, while D2-MSNs support action suppression, and the balance between these pathways is crucial for cognitive flexibility[25]. Corticostriatal synapses display long-term potentiation (LTP) and depression (LTD), as well as metaplasticity and homeostatic plasticity, which are experience-dependent and can remodel decision-making strategies[26]. Dysregulation of these plasticity rules has been linked to vulnerability to addiction and other psychiatric conditions[27].

mPFC-nucleus accumbens (NAc)

The prefrontal cortex (PFC) plays a central role in executive control and supports goal-directed behaviors, such as planning and initiating actions to obtain reward-related outcomes, including drug use[28]. Different PFC subregions project to distinct parts of the nucleus accumbens (NAc); for instance, the infralimbic (IL) mPFC primarily targets the NAc shell, while the prelimbic (PL) mPFC projects to the NAc core[29]. Studies using pharmacological and optogenetic tools have revealed that these distinct projections show subregion-specific differences in synaptic plasticity and cocaine-related behavioral outcomes[30,31].

Studies indicate that the glutamatergic pathway between the PFC and NAc undergoes plastic changes in rodent models of addiction and plays a key role in drug-seeking behavior after abstinence or extinction following prolonged cocaine exposure[32,33,34]. However, the effects within the mPFC vary depending on the subregion involved[32,33,34]. Activation of the PL-NAc projection is known to support reinstatement behavior after extinction, while inactivation of the IL-NAc circuit can also trigger reinstatement[32,33,34]. Comparable results have been reported in studies using forced withdrawal models under the cocaine incubation paradigm[35]. Although both the PL-NAc and IL-NAc circuits show similar neuroplasticity, optogenetic reversal of plasticity leads to opposite behavioral effects. Specifically, reversing ILNAc plasticity increases the incubation of cocaine craving, whereas reversing PLNAc plasticity reduces it[23].

The involvement of glutamatergatergic regulation of the NAc in addiction is well-established, but the roles of specific inputs are complex and context-dependent. Results differ depending on the specific PFC region examined (PL, IL, or orbitofrontal), the paradigm and time point related to cocaine (reinstatement, resistance to punishment, seeking, or escalation), the stimulation parameters, and the species studied[24,36]. Recent anatomical mapping further highlights a layer-specific distribution of mesolimbic projections from the mPFC. NAc-projecting neurons are enriched in upper layers (L2/35a) and display distinct molecular signatures, whereas deeper layers (L5b6) preferentially contribute to projections toward other mesolimbic targets such as the VTA or BLA[37,38]. This laminar organization provides additional mechanistic insight into how cortico-striatal and cortico-amygdalar pathways selectively gate information flow.

mPFC-Thalamus

mPFC exerts control over actions driven by and directed toward desired outcomes through its connections with various thalamic

nuclei[39] and recurrent networks involving the basal ganglia and thalamus[40]. This circuitry has evolved in vertebrates and is associated with the neural systems underlying higher-level cognitive processes in humans[41].

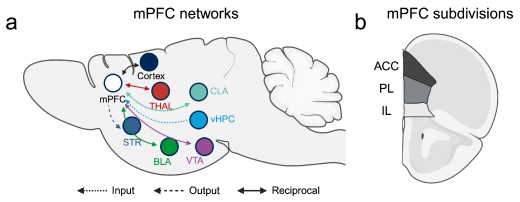

Fig. 1 The rodent medial prefrontal cortex (mPFC) networks and subdivisions. (a) Key brain regions that communicate with the mPFC. (b) Distribution of the subdivisions of the mPFC. Abbreviations: ACC, anterior cingulate cortex; BLA, basolateral amygdala; CLA, claustrum; IL, infralimbic; PL, prelimbic; STR, striatum; THAL, thalamus; vHPC, ventral hippocampus; VTA, ventral tegmental area, adapted from Anastasiades and Carter, 2021[11]. Images were created with Biorender.

The afferent and efferent connections between the mPFC and multiple nuclei in the central thalamus are present throughout all regions of the mPFC[42]. These higher-order thalamic nuclei primarily receive input from the cortex and are structured to facilitate particular components of adaptive, goal-directed behavior[42]. The mediodorsal nucleus (MD) receives strong excitatory projections from layer 5 and modulatory projections from layer 6 of the mPFC[43,44]. Thalamic projections are focused on the middle layers of the mPFC, while sparser diffuse projections are observed in layer I[43,44]. These thalamocortical projections activate excitatory networks and feedforward inhibition in the mPFC[43,44]. Recent evidence suggests that the MD nucleus enhances cortical connectivity and regulates the signal-processing properties of mPFC neurons through specific subpopulations of thalamocortical neurons that compensate for uncertainty related to low signals or high levels of noise[45,46].

Building on this, recent studies suggest that subpopulations of the mediodorsal (MD) thalamus may project selectively to different cortical layers of the mPFC. Inputs to superficial layers (L2/3) tend to engage recurrent excitatory networks, whereas inputs to deeper layers (L5) preferentially influence long-range output neurons, indicating layer-specific modes of thalamocortical communication[11]. This layer-specific targeting suggests that MDmPFC communication does not simply amplify cortical signals, but dynamically shapes information processing depending on behavioral context[11].

In summary, the mPFC is connected to several thalamic nuclei that contribute to different aspects of goal-directed behavior[42]. The MD provides focused input to the middle layers of the mPFC and is known to enhance and sustain activity in neurons involved in encoding action-outcome relationships[43,44]. This activity supports rapid learning, complex decision-making, and working memory[43,44]. In addition, the intralaminar nuclei send projections to both the basal ganglia and the cortex, helping regulate information flow in cortico-basal ganglia circuits[45,46]. Lesions in these regions have been shown to broadly affect functions that rely on the mPFC and striatum[45,46].

ventral Hippocampus (vHPC)- mPFC

Hippocampal input to the medial prefrontal cortex (mPFC) plays a role in providing contextual information, encoding memories, and regulating emotions[47,48]. Although the function in memory encoding and retrieval in HPC and mPFC has been well-established, it remains unclear which specific phases of memory functions (encoding, maintenance, and/or retrieval) require the interaction between the mPFC and the hippocampus[47]. Recent studies using projection-specific optogenetic silencing approach in rodents have supported the idea that the direct pathway from the hippocampus and subiculum to the mPFC is critically involved in regulating both cognitive and emotional aspects of memory[47]. Inhibiting the direct input from the ventral hippocampus (vHPC) to the mPFC impaired the encoding of location cues required for task performance, while maintenance and retrieval processes remained intact[47]. Moreover, the firing of goal-selective neurons in the mPFC was found to depend exclusively on the vHPC direct input during the encoding phase of each trial[47]. Additionally, the transmission of task-related information through the vHPC-mPFC projection may be supported by the synchronization of mPFC activity with gamma oscillations in the vHPC. Together, these findings suggest that direct input from the vHPC to the mPFC plays a critical role in encoding spatial cues during spatial working memory tasks[47].

Consistent with these findings, recent work supports the idea that interactions between vHPC and mPFC circuits involve oscillatory synchronization. In rodents, hippocampal theta-mPFC coherence is correlated with successful spatial working memory performance[49]. Cross-frequency coupling, such as theta-gamma coupling between hippocampus and mPFC, further suggests a mechanism by which contextual information might be coordinated with executive control[49]. Dysregulation of such synchrony has been implicated in stress-related disorders, underscoring the dynamic rather than static nature of prefrontal circuits[50].

The vHPC, mPFC, and basolateral amygdala (BLA) are also important regions in the regulation of anxiety-related behavior[48]. Among these, the projection from the vHPC to the mPFC has been implicated in processing aversive experiences[48]. To examine this further, one study combined multi-site neural recordings with optogenetic inhibition of vHPC terminals[48]. Inhibiting the

input from the vHPC to the mPFC altered anxiety responses and disrupted the mPFCs representation of aversive stimuli, along with reducing theta synchrony in a pathway-, frequency-, and task-specific manner[48]. Notably, bilateral inhibition of this projection induced physiological changes in the BLA associated with a state reminiscent of safety[48]. These results provide valuable insights into the distinct role of the vHPC-mPFC projection in anxiety-related behavior and the spatial representation of aversive information within the mPFC.

mPFC-Basolateral amygdala (BLA)

Fear extinction memory retrieval has been linked to increased neuronal activity in the medial prefrontal cortex (mPFC)[51]. However, how these extinction-related changes in the mPFC influence the amygdala to reduce fear responses is not fully understood[51]. One study used ex vivo electrophysiology combined with optogenetics to explore this question[51]. The results showed that fear extinction reduced the strength of excitatory synaptic transmission from the mPFC to the basolateral amygdala (BLA), as measured by glutamatergic excitatory postsynaptic currents (EPSCs), while inhibitory responses remained unchanged[51]. In contrast, the strength of mPFC input to intercalated neurons was unaffected by extinction[51]. The study also found that stimulating mPFC afferents caused heterosynaptic inhibition of auditory cortical inputs to the BLA[51]. Together, these findings suggest that fear extinction may weaken mPFCBLA excitatory signaling, helping to reduce amygdala output, while maintaining the function of inhibitory intercalated neurons that regulate fear expression[51].

The dysregulation of prefrontal control over the amygdala is implicated in the development of psychiatric disorders such as depression and anxiety. In a rodent anxiety model induced by chronic restraint stress (CRS), mPFC-BLA dysregulation has occurred. To be specific, the dysregulation primarily occurs in basolateral amygdala (BLA) projection neurons that receive one-way inputs from the dorsomedial prefrontal cortex (dmPFC→BLA PNs), rather than those with reciprocal connections to the dmPFC (dmPFC↔BLA PNs). Specifically, CRS leads to a shift in the excitatory-inhibitory balance driven by the dmPFC towards excitation in the dmPFC→BLA PNs, while the balance remains unaffected in the latter population. This specific dysregulation is associated with enhanced presynaptic glutamate release, which is primarily observed in the connections made by the dmPFC. Furthermore, this dysregulation is highly correlated with increased anxiety-like behavior in mice subjected to chronic stress[52]. Notably, low-frequency optogenetic stimulation of dmPFC inputs in the BLA effectively normalizes the enhanced glutamate release onto dmPFC→BLA PNs and leads to a lasting reduction in anxiety-like behavior induced by CRS. These findings highlight a target cell-specific dysregulation in the transmission from the mPFC to the amygdala in response to stress-induced anxiety[52]. A more recent study regarding the subcircuits established by the mPFC neurons in a rodent anxiety model induced by CRS showed that CRS has been found to have a significant impact on the synaptic transmission in the dorsomedial prefrontal cortex (dmPFC) layer V neurons that project to the BLA. Specifically, CRS results in a reduction of inhibitory synaptic transmission onto these BLA-projecting neurons, while excitatory synaptic transmission remains unaffected. This disruption in the balance between excitation and inhibition (E-I balance) leads to an overall increase in excitation. Additionally, CRS selectively increases the intrinsic excitability of the BLA-projecting neurons in dmPFC layer V[38].

In addition to direct excitatory control, mPFC projections to the BLA can indirectly regulate fear expression by engaging intercalated cell (ITC) clusters, which mediate feedforward inhibition of BLA principal neurons[51,53]. Under chronic stress, this gating mechanism becomes disrupted, leading to excessive excitatory drive from mPFC to BLA and heightened anxiety-like behavior[52]. Together, these findings highlight the state-dependent modulation of amygdala output by mPFCITC interactions[54].

Discussion

The medial prefrontal cortex (mPFC) integrates a wide range of cognitive functions through complex and flexible neural circuits. The mPFC is primarily composed of excitatory pyramidal neurons (∼80–90%) and inhibitory GABAergic interneurons (∼10–20%), which together form the basis of its functional connectivity . These neurons create long-range projections to several brain regions, constructing dynamic circuits that allow the mPFC to update, coordinate, and modulate behavior based on both internal goals and external stimuli.

In addition to pyramidal neurons, the mPFC contains diverse subtypes of inhibitory interneurons, including parvalbumin-, somatostatin-, and vasoactive intestinal peptide-expressing cells, which differentially shape local circuit dynamics and long-range communication[55]. Beyond classical glutamatergic and GABAergic mechanisms, modulatory systems further refine mPFC function. For instance, endocannabinoid signaling regulates prefrontal excitatory transmission and plasticity[56]. Likewise, cholinergic inputs tune prefrontal theta rhythms and attentional control, providing another layer of oscillatory modulation[57]. Together, these modulators highlight that mPFC circuits are not static entities but are dynamically regulated by diverse cellular and neurochemical influences.

Each mPFC-related circuit contributes differently to cognitive function. For instance, the mPFCDMS circuit plays a role in attention and behavioral inhibition, the mPFC-NAc circuit is involved in reward-driven behavior and drug-seeking, and the vHPC-mPFC circuit enables spatial memory encoding and emotional regulation. Meanwhile, the mPFC-BLA and mPFC-thalamus circuits are essential for fear/anxiety modulation and

working memory, respectively. Most of these circuits interact in reciprocal loops rather than functioning independently, allowing the mPFC to process cognitive functions with greater flexibility and context sensitivity.

Consistent with this, growing evidence has supported that the dysregulation of these circuits has been associated with psychiatric disorders, such as anxiety disorders, depression, and addiction. The mPFC is among the last cortical regions to mature, continuing into late adolescence. This protracted development renders it sensitive to neurodevelopmental disorders such as ADHD and schizophrenia[58]. With aging, mPFC-dependent working memory declines, partly due to reduced synaptic integrity[59]. However, the exact mechanisms remain inconclusive; excessive excitation, reduced inhibition, or altered synaptic plasticity could be the possible mechanisms for these diseases. Understanding these physiological pathways not only enhances our apprehension of normal cognitive processes but also reveals pathways for future therapeutic approaches.

In addition to neuronal mechanisms, non-neuronal cells such as astrocytes regulate glutamate uptake and release signaling molecules such as D-serine, thereby fine-tuning the excitatory/inhibitory balance within mPFC circuits[60]. Microglia contribute to synaptic pruning and plasticity, influencing circuit maturation and stress reactivity[61].

To study these complex interactions, researchers increasingly rely on advanced circuit-mapping tools. While optogenetics provides millisecond precision in controlling defined cell types, it can artificially synchronize activity beyond physiological levels[62]. Chemogenetics offers cell-type selectivity but with slower temporal resolution[63]. Ex vivo electrophysiology provides mechanistic insight but cannot fully capture in vivo dynamics, whereas local field potentials (LFPs) reflect population synchrony without single-cell resolution[64]. Emerging techniques such as fast-scan cyclic voltammetry and fiber photometry enable sub-second measurement of neurotransmitter dynamics, although fiber photometry lacks single-cell resolution[65 66]. Complementary approaches like miniature microendoscopes (miniscopes) now enable longitudinal single-cell calcium imaging in freely moving animals, providing a more detailed view of circuit function[67]. Further research should aim to map these circuits in more detail, especially using cell-type-specific tools and longitudinal studies in both healthy and disease models. Ultimately, connecting circuit-level findings to behavior provides a promising route for bridging neuroscience and mental health treatment. Such insights may also inform novel therapeutic strategies, including pharmacological interventions and non-invasive neuromodulation approaches (e.g., rTMS, tDCS) that target prefrontal circuits implicated in psychiatric disorders[68].

Beyond rodent studies, emerging approaches such as postmortem human mPFC transcriptomic profiling[69] (e.g., Allen Brain Atlas), primate and marmoset fMRI connectivity studies[70], and intracranial electrophysiology[71] provide critical complementary perspectives. Although this review mainly focuses on circuitry studies using rodents, acknowledging their contributions highlights the translational bridge between basic circuit findings and human psychiatric research. Nevertheless, it is important to note that rodent anxiety-like behaviors only partially model human depression and anxiety, and thus, translational interpretations should remain cautious.

Methods

A focused literature review was conducted to examine how the medial prefrontal cortex (mPFC) contributes to cognition and behavior in rodents. PubMed and Google Scholar were used to search for peer-reviewed, English-language articles published from 2000 onward. Search terms included medial prefrontal cortex, mPFC and cognition, mPFC and decision-making, prefrontal cortex and emotion, and rodent prefrontal cortex circuits. Studies were selected if they used rodent models, described mPFC connections to other brain regions, and investigated cognitive functions such as memory, attention, decision-making, or emotion. Experimental methods included optogenetics, chemogenetics, tract-tracing, and electrophysiology. For each study, information was collected on the species used, the mPFC subregion studied, the techniques applied, and the behavioral or physiological results. The review focused on circuits between the mPFC and the dorsomedial striatum (DMS), nucleus accumbens (NAc), thalamus, ventral hippocampus (vHPC), and basolateral amygdala (BLA). These circuits were grouped by functions to help summarize current understanding and identify areas for future research.

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Table 1 Summary of medial prefrontal cortex (mPFC) long-range circuits, species, layers, methods, behavioral roles, and representative studies

Circuits	Species	Layers (if known)	Methods	Main behavioral effect	Representative references	Caveats / notes
mPFC → DMS	Mouse, Rat	L5 projection neurons	Optogenetics, Chemogenetics, Electrophysiology, Tracing	Attentional control, inhibitory control of premature responses	[16,17,22]	Effects are task-dependent; PL vs IL subdivisions may differ
mPFC → NAc	Mouse, Rat	L2/3–5a (NAc-projecting neurons)	Optogenetics, Electrophysiology, Tracing	Drug-seeking reinstatement, incubation of cocaine craving, goal-directed behavior	[30,32,37]	Subregion-specific effects (PL vs IL); circuit roles depend on drug paradigm
mPFC ↔ MD Thalamus	Mouse, Rat	Inputs to L2/3, outputs from L5–6	Tracing, Electrophysiology	Working memory, actionoutcome encoding, decision-making	[43,44,11]	Subpopulations of MD neurons shape signals differently (uncertainty, noise)
vHPC → mPFC	Mouse, Rat	L2/3 recipient neurons	Optogenetics, Electrophysiology	Spatial working memory encoding, thetagamma synchrony, anxiety regulation	[47,48,49]	Theta/gamma synchrony is state- and task-dependent
mPFC → Intercalated cells (ITC, amygdala)	Mouse	L5 projections via ITCs	Optogenetics	Fear gating, inhibitory control of BLA output	[53,54]	Stress paradigms vary; ITC gating underexplored

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