Review

Circuit organization of the rodent medial prefrontal cortex

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The prefrontal cortex (PFC) orchestrates higher brain function and becomes disrupted in many mental health disorders. The rodent medial PFC (mPFC) possesses an enormous variety of projection neurons and interneurons. These cells are engaged by long-range inputs from other brain regions involved in cognition, motivation, and emotion. They also communicate in the local network via specific connections between excitatory and inhibitory cells. In this review, we describe the cellular diversity of the rodent mPFC, the impact of long-range afferents, and the specificity of local microcircuits. We highlight similarities with and differences between other cortical areas, illustrating how the circuit organization of the mPFC may give rise to its unique functional roles.

Cell- and synapse-specific wiring rules in the mPFC

The PFC plays an essential role in higher brain function, including cognition, motivation, reward, and emotion [1,2]. Dysfunction of the PFC is also implicated in diverse neuropsychiatric disorders, including schizophrenia, attention deficit hyperactivity disorder (ADHD), addiction, and depression [3,4]. The behavioral and computational roles of the rodent mPFC have been extensively studied for several decades. However, our understanding of cortical circuitry has predominantly emerged from studies of primary sensory cortices [5,6]. Importantly, the mPFC displays a distinct architecture [7], potentially enabling different forms of processing. In particular, the mPFC receives a variety of long-range excitatory inputs and sends diverse outputs to many other brain regions (Figure 1A). These input and output pathways are connected via the local circuit, in which different excitatory and inhibitory neurons communicate with each other through specific wiring rules.

Recent work using a variety of approaches has made significant strides towards revealing the specificity of mPFC circuits. Anatomical tracing of mPFC afferents and efferents has characterized highly organized brain networks [8–13]. While some connections are unidirectional, most are organized as reciprocal loops, allowing the mPFC to orchestrate diverse behaviors across time by continually updating neural activity [14,15]. Slice electrophysiology and optogenetics have enabled mechanistic dissection of local and long-range circuits [16]. Many connections are highly specific, with the identity of presynaptic and postsynaptic cells determining signal flow within the network. Last, *in vivo* electrophysiology, imaging, optogenetics, and chemogenetics have shown how individual cell types and connections contribute to behavior and disorders [17–21]. Here we review recent progress in understanding the circuit organization of the mPFC in rodents, focusing on emerging rules of cell- and synapse-specific connectivity. Some variations exist in the literature with regard to the precise definition of the rodent mPFC, and for the purpose of this review the mPFC refers to the collection of the anterior cingulate (ACC), prelimbic (PL), and infralimbic (IL) cortices. Much of the work on cell type-specific circuit mapping of the mPFC has been conducted so far in mice, due to the availability of genetic tools in this model. Accordingly, the discussions in this review focus primarily on the mouse mPFC and particularly on the PL. Examining whether and how these findings generalize to other species remains an important goal for future research.

Highlights

The rodent medial prefrontal cortex (mPFC) shows key differences from sensory cortex in the composition and organization of local and long-range circuits.

Long-range inputs from other brain regions display distinct lamination patterns, which contribute to the cellular and subcellular targeting of these projections.

Long-range inputs to the mPFC contact distinct populations of both projection neurons and interneurons, potentially explaining these inputs' unique behavioral roles.

In many cases, long-range inputs preferentially target neurons that project back to the input region, providing a synaptic substrate for strong reciprocal loops.

Projection neurons and interneurons also make specific local connections that shape how functional signals are routed through the mPFC, linking inputs with outputs.

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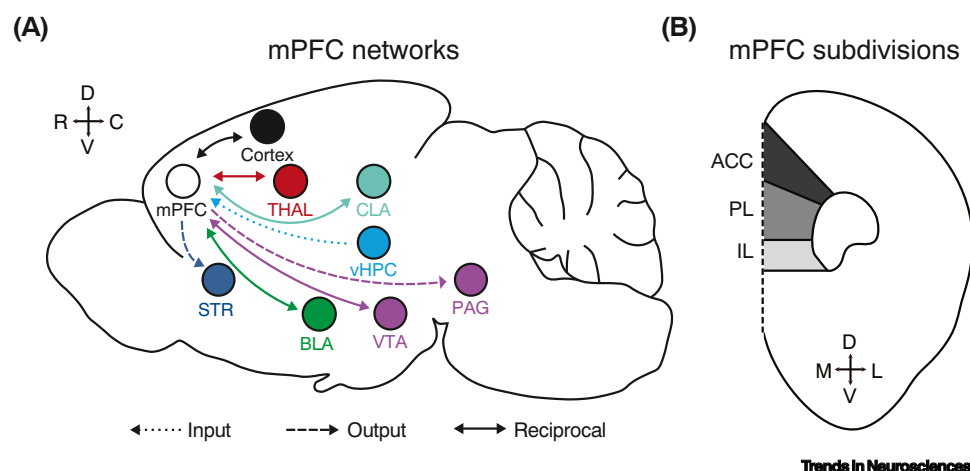adam.carter@nyu.edu (A.G. Carter).

Figure 1. General organization of the rodent medial prefrontal cortex (mPFC). (A) Key brain regions that communicate with the mPFC, by providing input, receiving output, or making reciprocal connections. (B) Distribution of the subdivisions of the mPFC along the dorsoventral axis. Abbreviations: ACC, anterior cingulate cortex; BLA, basolateral amygdala; CLA, claustrum; IL, infralimbic; PAG, periaqueductal gray; PL, prelimbic; STR, striatum; THAL, thalamus; vHPC, ventral hippocampus; VTA, ventral tegmental area.

General organization of the mPFC

The cerebral cortex is organized into layers, in which neurons sample long-range inputs and interact via local connections [5,6]. The sensory cortex is divided into six main layers, whose structure and function are broadly conserved across modalities. Layer (L)1 contains the apical dendrites of pyramidal neurons and several populations of GABAergic interneurons [22–24]. L2 and L3 are typically grouped as L2/3, containing intratelencephalic (IT) cells that project to other cortical regions [25,26]. L4 is a major input layer, with either pyramidal cells or stellate cells that make local connections within the cortex. L5 is a major output layer, with a separate group of IT cells and pyramidal tract (PT) cells that target subcortical regions [5,27]. L6 is another output layer, home to the corticothalamic (CT) cells that project to thalamic relay nuclei and the thalamic reticular nucleus (TRN) [27,28]. A variety of interneurons are distributed across L1 to L6, including parvalbumin (PV+), somatostatin (SOM+), and vasoactive intestinal peptide (VIP+) cells [5,29]. There are well-defined rules for connections between pyramidal cells and interneurons within and across layers [5]. Long-range inputs also target specific layers, with primary thalamic inputs to L4 and L5b, higher-order thalamic inputs to L1 and L5a [5,30], and cortical inputs to superficial and deep layers, depending on the hierarchical relationships between connected cortical regions [5].

There are several major differences between this traditional laminar view of the sensory cortex and the rodent mPFC. First, the mPFC is agranular, lacking a canonical thalamo-recipient L4 and instead possessing inputs across L1, L2/3, L5, and L6. Consistent with the lack of L4, there is minimal ROR-beta labeling in the mPFC, which defines this layer in the sensory and motor cortices [5,31]. Second, projection neurons are located across L2 to L6, which often engage in reciprocal circuits with other brain regions. This includes multiple types of IT, PT, and CT cells, which also communicate with each other via local excitation [5,16,26,32,33]. Third, there are different allocations of GABAergic interneuron subtypes, which mediate local inhibition [34]. There appear to be fewer PV+ cells but more SOM+ cells, which may give rise to differences in local computations. Fourth, long-range inputs arrive across L1 to L6, which convey signals related to action, cognition, reward, and emotion. These inputs contact and drive projection

neurons and interneurons, with wiring rules depending on presynaptic and postsynaptic cells. Understanding mPFC computations therefore requires a detailed knowledge of cell types, activation by long-range inputs, and processing via local circuits. In many cases, determining the intrinsic physiology of individual cells and synaptic properties of specific connections is critical to assess the organization of these networks.

It is important to note that the rodent mPFC comprises multiple regions, including ACC, PL, and IL (Figure 1B), whose roles in cognition gradually shift along the dorsoventral axis, from decision making and action to motivation and emotion. They also have distinct inputs and outputs, with differences in connectivity likely underlying behavioral roles. Comparison of the PFC across species is an active area of debate [35–37] and beyond the scope of the current review. However, the rodent mPFC shares many features with the medial agranular cingulate cortex of humans and primates and is considered to be distinct from the dorsolateral PFC. In this review, we focus primarily on the mouse PL, where most studies on cell type-specific circuitry have been performed, drawing comparisons with ACC, IL, and other cortical areas whenever possible.

Diversity of projection neurons in the mPFC

The mPFC possesses a variety of excitatory projection neurons that span multiple layers and target diverse brain regions. These projection neurons allow the mPFC to influence activity in other parts of the brain and exert top-down control of behaviors. Recent work highlights the properties of these cells and the rules by which they respond to excitatory and inhibitory inputs.

Across the cortex, the three main subclasses of projection neurons are IT, PT, and CT cells, which can be readily identified by retrograde labeling [5] (Figure 2A). These cells have stereotyped morphology and intrinsic physiology [5] (Figure 2B,C) and have distinct gene expression profiles that allow genetic access [38]. However, expression profiles in the mPFC often differ from elsewhere in the cortex, with major markers often failing to assume characteristic lamination patterns. Moreover, the traditional IT/PT/CT categorization is clearly an oversimplification of projection neuron diversity. Instead, individual neurons send axon collaterals to multiple targets, but not all neurons in a given class project to all known targets of that class [25,39]. Thus, each population can be further subdivided based on their projection targets, laminar location, and connectivity.

IT cells in the mPFC are present across L2–L6 and project to other parts of the cortex, basolateral amygdala (BLA), striatum, and claustrum (Figure 2A). As seen in other cortices [25,26], L2/3 IT cells segregate into distinct output pathways, with cortico-amygdalar neurons distinct from corticocortical or corticostriatal neurons [40,41]. L5 and L6 IT cells have morphologies and physiology markedly distinct from nearby L5 PT and L6 CT cells [42–44] (Figure 2B,C). The axons of L5 IT cells branch to many regions, comprising corticocortical, corticostriatal, cortico-amygdalar, and corticoclaustral projections [20,32]. While also present in other cortices, corticostriatal and corticoclaustral neurons appear more numerous and broadly distributed across layers in the mPFC [32,45,46]. Last, the mPFC sends strong, bilateral projections to both the ipsi- and contralateral claustrum, which appears unique to the frontal cortex [47].

Across the cortex, PT cells are confined to L5b (Figure 2A), with elaborate dendrites and elevated HCN channel expression [42–44] (Figure 2B,C). PT cells in the mPFC target diverse subcortical brain regions, including ipsilateral striatum, thalamus, pons, periaqueductal gray, and multiple neuromodulatory centers [16,48]. These diverse outputs are an important feature of the mPFC, which allows PT cells to influence multiple aspects of higher-order behavior. In motor cortex,
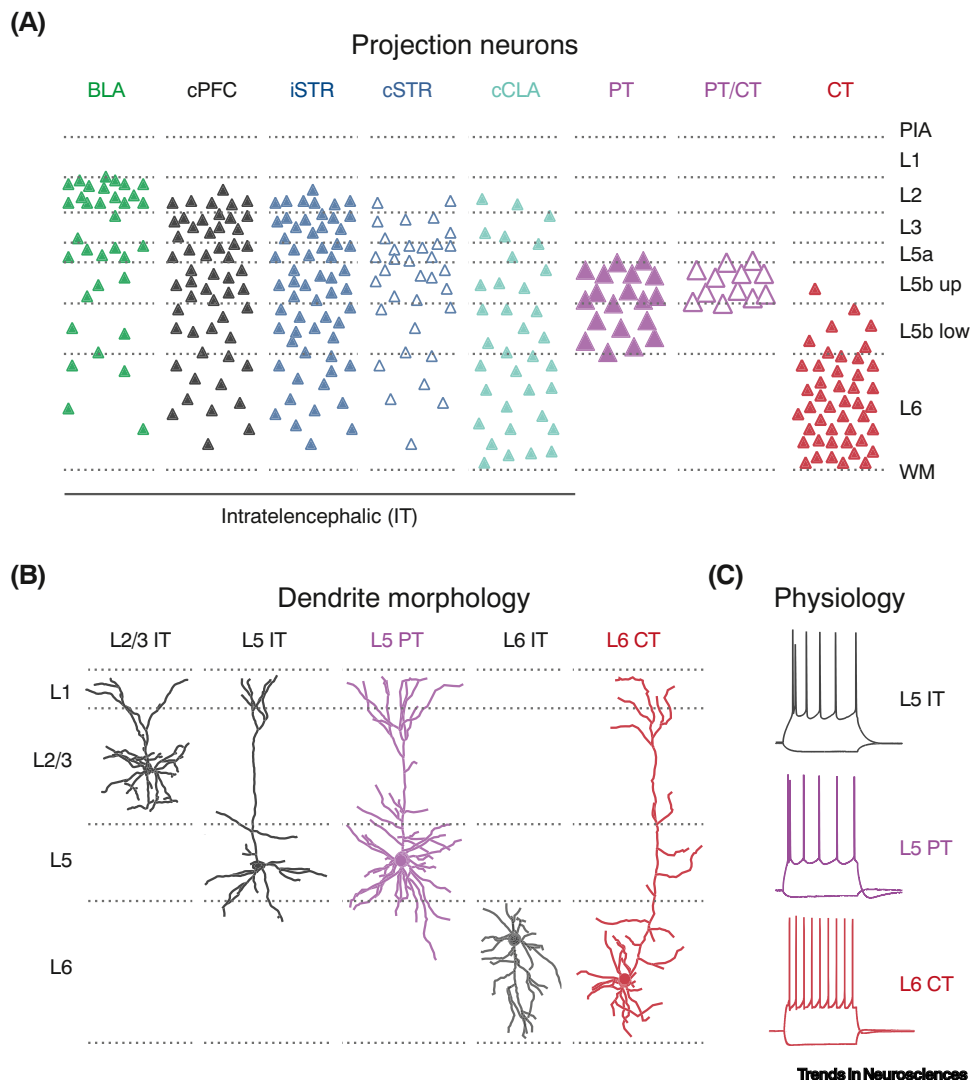
Figure 2. Medial prefrontal cortex (mPFC) projection neuron diversity. (A) Laminar distributions of projection neurons in the mPFC, identified by the injection of retrograde tracers into target brain regions. Note that projection neurons are found from L2 to L6. (B) Dendritic morphologies of mPFC projection neurons. From left to right: L2/3 intratelencephalic (IT) cell, L5 IT cell, L5 pyramidal tract (PT) cell, L6 IT cell, and L6 corticothalamic (CT) cell. Note that L5 PT cells have more elaborate dendrites than adjacent IT cells and that L6 CT cells have apical dendrites that often extend to L1, unlike L6 IT cells that can display inverted pyramidal morphologies. (C) Intrinsic firing properties of mPFC projection neurons. From top to bottom: L5 IT cells, L5 PT cells, and L6 CT cells. Note that L5 IT cells lack Ih-mediated voltage sag, L5 PT cells display strong Ih-mediated voltage sag, and L6 CT cells display highly nonadapting firing patterns. (A) Adapted from [16,32]. Data in (B,C) used, with permission, from [16,32,42]. Abbreviations: BLA, basolateral amygdala; cCLA, contralateral claustrum; cPFC, contralateral PFC; cSTR, contralateral striatum; CT, corticothalamic, non-PT cells; iSTR, ipsilateral striatum; IT, intratelencephalic; l5b up, upper layer (L)5b; L5b low, lower L5b; PIA, pial surface; PT, pyramidal tract; PT/CT, PT cells that send collaterals to the thalamus; WM, white matter.

PT cells fall into two subpopulations, with upper L5b innervating the pons and thalamus and lower L5b bypassing the thalamus to target the medulla and spinal cord [39]. While PT cells in upper L5b of the mPFC also target thalamus [16], the targets of lower L5b have not been fully explored, but are expected to include different sets of neuromodulatory, midbrain, and hindbrain areas [48].

Last, L6 CT cells are distinguished by their distinct morphology and highly nonadapting firing properties [16,27] (Figure 2A–C). The apical dendrites of CT cells in the mPFC extend to the pial surface, suggesting they sample inputs across all layers. Projection neurons in L5 and L6 target multiple thalamic nuclei, including both mediodorsal (MD) and ventromedial (VM) thalamus. The release properties of L5 PT and L6 CT inputs to thalamus follow the 'driver' and 'modulator' classification seen in sensory thalamus, respectively [16]. Interestingly, a subset of both PT and CT cells sends bifurcating projections to both MD and VM [16], an arrangement not typically found in sensory cortex. CT cells also target TRN to drive inhibition of thalamus, which may regulate attention [28,49]. Last, L6 CT cells are interspersed with L6 IT cells, which again lack HCN channels and often have unusual multipolar or even inverted dendritic morphologies, suggesting they receive distinct afferents (Figure 2A–C).

Long-range inputs to the mPFC

The mPFC processes long-range inputs from many other brain regions, including other cortical areas, thalamus, BLA, ventral hippocampus (vHPC), and claustrum (Figure 3A). *In vivo* studies highlight distinct functional roles for these afferents in cognitive and emotional behavior [50–53]. Slice recordings also show how each input preferentially activates specific types of projection neurons in the mPFC.

Inputs from the contralateral PFC (cPFC) support prefrontal activity and share information between hemispheres [54]. cPFC inputs are distributed across all layers (Figure 3A) and contact IT cells in superficial and deep layers [40,55,56], cortico-amygdalar neurons in L2 [40], and PT cells in L5 [42,57] (Figure 3B). Overall, cPFC connectivity appears relatively egalitarian, making similar-strength connections onto L2 cortico-amygdalar and corticocortical neurons (Figure 3C). Differences in the targeting of L5 IT and PT cells are compensated by differences in input resistances, yielding responses of similar amplitude [42,57]. The subcellular targeting of cPFC synapses is also largely uniform across the dendrites of L2 and L5 pyramidal neurons [42,55,57]. However, an important caveat is that previous work has considered the entirety of callosal input, and it may be that IT cells residing in different layers contact distinct targets in the contralateral hemisphere.

Thalamic inputs to the mPFC support a wide array of cognitive functions, including working memory, learning, attention, and arousal [50,51,58,59]. While most work has focused on MD thalamus, inputs arise from several nuclei, including VM thalamus [10,11,16,23]. MD inputs terminate in two prominent bands of axons found in L1 and L3 (Figure 3A). MD input strongly engages L3 IT cells, which are readily driven to fire action potentials [16] (Figure 3B). This input also contacts L5 pyramidal cells, preferentially targeting the soma of IT cells over nearby PT cells (Figure 3C). In principle, this may ensure that thalamic inputs are processed locally by the mPFC before being relayed back to the thalamus. However, MD input to deep L1 (L1b) also contacts the apical dendrites of L5 PT cells (Figure 3C). Ultimately, MD has a variety of influences on both the superficial and deep layers of mPFC, but appears to primarily activate L3 IT cells, which may help to support local processing via recurrent interactions in the local circuit [14].

By contrast, VM inputs to the mPFC terminate in a dense band in superficial L1 (L1a), similar to other 'matrix' thalamic inputs (Figure 3A). VM inputs are relatively weak at IT cells in L2 to L5 [16,60] (Figure 3B). Instead, VM inputs are highly enriched at the distal apical dendrites of PT cells [16,23], which is more pronounced than for MD inputs and not seen for other long-range inputs [42,57,61] (Figure 3C). This dendrite targeting could provide a powerful way for thalamic input to activate PT cells and thus enhance mPFC output [23]. Similar connectivity is seen for higher-order thalamic inputs to other frontal cortices [28], but equivalent inputs to somatosensory

(A)

Long-range inputs

(B)

Main projection targets

(C)
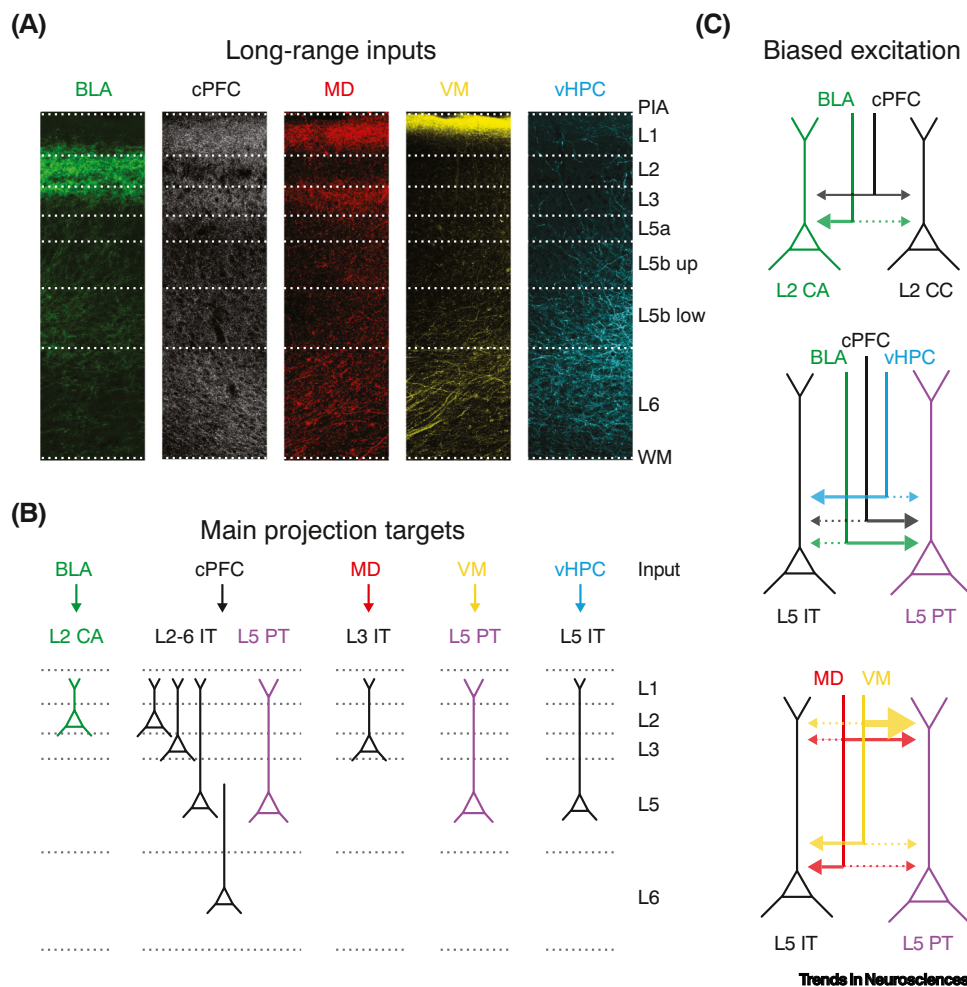
Biased excitation

Trends in Neurosciences

Figure 3. Long-range excitatory inputs to the medial prefrontal cortex (mPFC). (A) Laminar distribution of axons to the prelimbic mPFC from different brain regions. From left to right: BLA, basolateral amygdala; cPFC, contralateral PFC; MD, mediodorsal thalamus; VM, ventromedial thalamus; vHPC, ventral hippocampus. Note that inputs arrive in characteristic patterns across layer (L)1 to L6. (B) Summary of the main projection neurons contacted by long-range excitatory inputs. The BLA activates reciprocally projecting L2 cortico-amygdalar (CA) neurons. cPFC innervates more broadly, including L5 pyramidal tract (PT) cells and a range of intratelencephalic (IT) cells. MD strongly activates L3 IT cells, while VM engages the dendrites of L5 PT cells. vHPC primarily targets L5 IT cells. Note that the most strongly driven targets are shown for simplicity, but most inputs provide some excitation to all cells in the network. (C) Biased long-range excitatory inputs onto neighboring projection neurons. Top: BLA preferentially contacts L2 CA neurons over L2 corticocortical (CC) neurons, whereas cPFC shows no bias. Middle: BLA and cPFC preferentially contact L5 PT cells over L5 IT cells, with vHPC showing the opposite bias. Bottom: MD preferentially contacts L5 IT cells over L5 PT cells, but makes stronger contacts onto dendrites of L5 PT cells. VM inputs make highly enriched inputs to L5 PT apical dendrites, where they can evoke dendritic Ca^{2+} spikes. Images in (A) adapted, with permission, from [23] and unpublished data from the Carter laboratory.

cortex are not enriched onto PT apical dendrites [62], suggesting that this thalamic connectivity motif may be a distinguishing feature of higher-order frontal circuits. Last, the mPFC may have weaker thalamic input to L6 than the sensory cortex, with no prominent band of thalamic axons in deeper layers [16,30].

The mPFC also markedly differs from sensory cortices with major input from regions that convey emotional signals. Connections with the BLA are important for the encoding, expression, and

reversal of emotional states, including aversive memories [21,53]. BLA inputs are particularly enriched in L2 of PL (Figure 3A), where reciprocally connected cortico-amygdalar neurons are also prominent [40,48]. BLA inputs to mPFC selectively target cortico-amygdalar neurons over intermingled corticocortical or corticostriatal neurons, providing the synaptic basis for a strong reciprocal loop [40,41] (Figure 3B,C). However, BLA axons display pronounced differences along the dorsoventral axis, with more input to L2 of PL but L5 of IL [63]. Interestingly, BLA inputs are stronger at PT over IT cells in L5 of IL, as seen for callosal inputs but opposite to thalamic inputs [16,63] (Figure 3C). Biased connectivity is also seen in the reverse direction, with mPFC making stronger connections onto amygdalar-cortical cells in the BLA, providing a synaptic basis for strong, reciprocal connectivity between these regions [64].

Last, hippocampal input to the mPFC provides contextual information and plays a role in mnemonic encoding and emotional control [52,65] (Figure 3A). Hippocampal inputs arise from pyramidal cells in vHPC, including both CA1 and the subiculum [61]. Recent studies indicate a variety of projection cells in the vHPC, which have distinct physiological properties and connectivity [65]. vHPC inputs to the mPFC are region specific, targeting multiple layers in IL, largely restricted to L5 in PL, but mostly absent from ACC [61]. vHPC inputs are also layer specific, with the strongest input to pyramidal neurons in IL L5, followed by IL L2/3 and PL L5, with weak input to PL L2/3 and L6 [61] (Figure 3B). Finally, vHPC inputs are cell-type specific, targeting IT cells over PT cells in L5 of IL [61], which is similar to thalamic inputs but opposite to BLA and cPFC inputs (Figure 3C). The dorsal hippocampus also has a functional impact on the mPFC, but there are few direct connections, suggesting this influence is via polysynaptic circuits.

In addition to these main afferents, there are several other long-range inputs to the mPFC, including from the claustrum and inhibitory regions, about which relatively little is known. It will be important to assess which projection neurons are most strongly engaged by these inputs.

Local excitatory circuits in the mPFC

Once long-range inputs drive projection neurons in the mPFC, their influence also reflects local excitation. In sensory cortex, there is a canonical flow of excitation between layers, with L4 signaling to L2/3, which then signals to L5 (Figure 4A). While the equivalent organization has not been extensively studied in the mPFC, it is likely to be similar to other frontal and motor cortices, which also show a clear hierarchy of connectivity from superficial to deep layers (Figure 4A). For example, thalamo-recipient pyramidal cells in L3 send ascending connections to L2 pyramidal cells [31]. L2/3 pyramidal cells then make descending connections to L5 pyramidal cells, preferentially contacting PT cells [16,66]. In a further refinement, descending connections may also depend on the sublayer of presynaptic and postsynaptic cells [67,68]. For example, PT cells in lower L5b receive little local input and instead mainly process long-range afferents [69]. Moreover, L5 IT cells send ascending projections to L2/3, whereas L5 PT cells provide minimal feedback [70]. Little is currently known about connections onto IT and CT cells in L6, including how these neurons are engaged locally and influenced by long-range inputs [71].

Pyramidal cells also robustly communicate within individual layers, with wiring rules often determined by presynaptic and postsynaptic cell type [5,26,33] (Figure 4B). Connections within the same cell type may be particularly strong in the mPFC, displaying short-term dynamics predicted to sustain reverberant activity [72]. For example, robust connections between L2/3 pyramidal cells may amplify inputs arriving from MD [14]. Similarly, facilitation of connections between PT cells may ensure reliable output to subcortical targets [72]. Connections between cell types can also be highly selective, providing directionality of signaling within and between cortical layers. For example, IT cells strongly innervate PT cells, which may ensure that local computations are
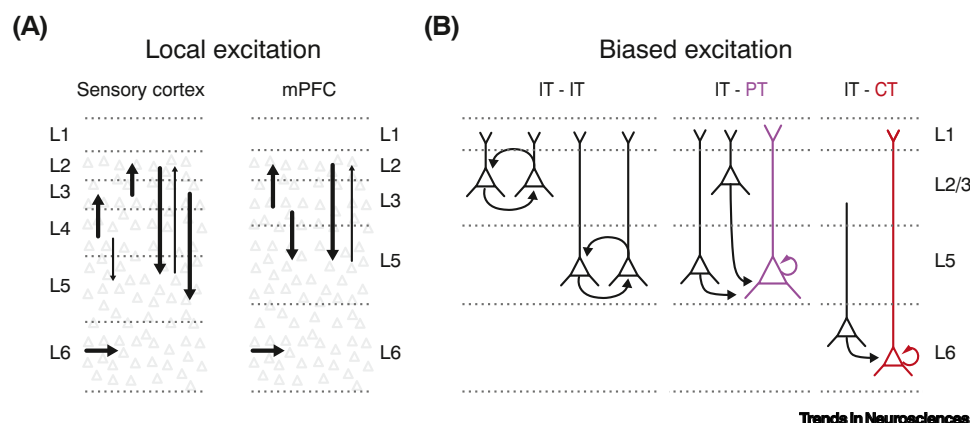
Figure 4. Local excitatory connections in the medial prefrontal cortex (mPFC). (A) Simplified wiring diagram of the local excitatory circuit in the sensory cortex (left) and mPFC (right). Individual arrows represent major excitatory connections, with the weight of the arrow indicating the connection strength. (B) Biased local excitatory connectivity within and across layers of the mPFC. Note that intratelencephalic (IT) cells, pyramidal tract (PT) cells, and corticothalamic (CT) cells make within-class connections and that IT cells also make between-class connections onto PT and CT cells, which are the major outputs to subcortical brain regions.

relayed via output pathways [5,16,33]. However, the reverse connection is weak, perhaps ensuring that output signals do not immediately re-enter the cortical network. Overall, both local and long-range inputs make precise connections onto specific projection neurons in the mPFC.

Interneurons and local inhibitory circuits in the mPFC

The ability of projection neurons to respond to long-range and local excitation is also strongly shaped by inhibitory interneurons, which are the subject of several reviews [29,73,74]. Across the cortex, GABAergic interneurons are divided into three largely nonoverlapping populations expressing PV, SOM, or serotonin receptor 3a (5HT3aR) [29] (Figure 5A). The latter are further subdivided by the expression of cholecystokinin (CCK), VIP, reelin, or neuron-derived neurotrophic factor (NDNF) [22,29]. All of these interneurons are found in the mPFC and display lamination patterns broadly similar to those of other cortical areas (Figure 5B). They also have characteristic physiological and morphological properties that determine how they respond to inputs and inhibit pyramidal cells (Figure 5C). However, recent work suggests that there may be important differences in the properties of interneurons in the mPFC [75]. For example, there appear to be fewer PV+ cells and more SOM+ and CCK+ cells than in other cortical areas [34,76,77]. The dearth of PV+ cells in superficial layers, particularly in the PL and IL, may instead be compensated by other interneurons. It remains unclear whether these differences reflect shifts in the relative ratios of cardinal interneuron subtypes, additional subtypes of interneurons in the mPFC, or some combination of factors.

Inhibitory connections onto pyramidal cells also display class-specific wiring rules at the cellular and subcellular levels [29] (Figure 6A). For example, PV+ cells inhibit near the soma and axons of nearby pyramidal cells and SOM+ cells primarily inhibit the dendrites, whereas VIP+ cells primarily target other classes of interneurons. Although not as well studied, CCK+ cells also target the soma of pyramidal cells and NDNF+ cells the distal apical tufts [23,24,77]. Recently, interneurons have been proposed to provide a 'blanket' of inhibition onto neighboring pyramidal cells [78]. However, in the mPFC, inhibitory connections neurons often show pronounced selectivity. In superficial layers, PV+ and SOM+ cells preferentially target L2 cortico-amygdalar over adjacent corticocortical and corticostriatal neurons [41,79] (Figure 6B). This biased connectivity is also
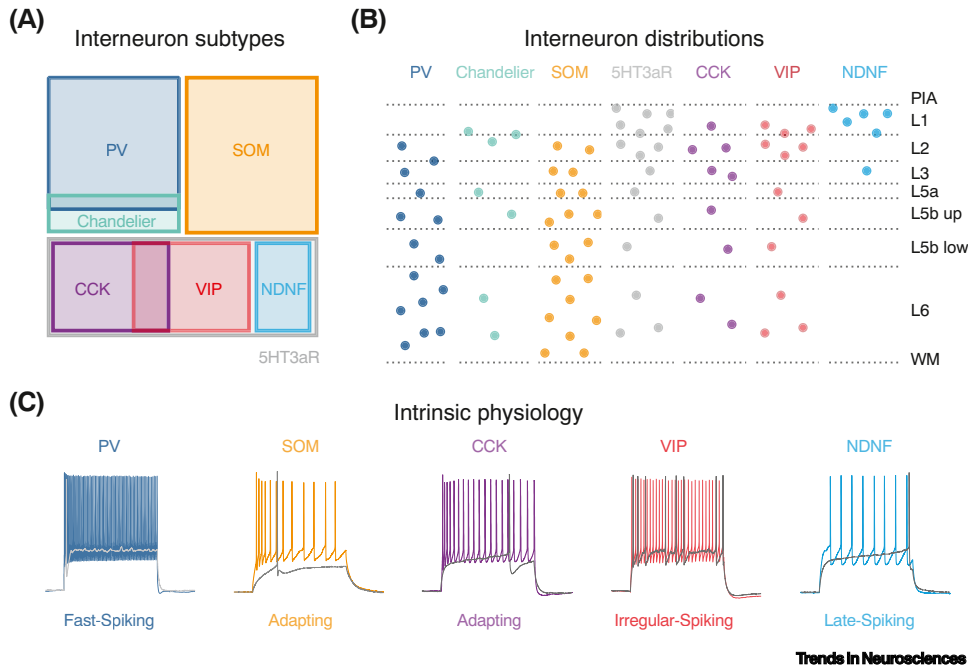
Figure 5. GABAergic interneuron subtypes in the medial prefrontal cortex (mPFC). (A) Segregation of different subpopulations of interneurons based on gene expression, morphology, and physiology. (B) Laminar distributions of interneurons based on labeling with transgenic mouse lines. (C) Characteristic firing properties of different interneurons. Gray traces show peri-threshold spikes and colored traces show sustained firing in response to larger current steps. Data in (B) adapted from [23,32,77,93]. Traces in (C) adapted, with permission, from [23] and unpublished data from the Carter laboratory. Abbreviations: 5HT3aR, serotonin receptor 3a; CCK, cholecystokinin; L5b low, lower layer (L)5b; L5b up, upper L5b; NDNF, neuron-derived neurotrophic factor; PIA, pial surface; PV, parvalbumin; SOM, somatostatin; VIP, vasoactive intestinal peptide; WM, white matter.

seen in deeper layers, where PV+, SOM+, CCK+, and NDNF+ interneurons all preferentially target L5 PT cells over neighboring IT cells [23,42,56,77] (Figure 6B). Nevertheless, it remains uncertain whether this biased connectivity reflects distinct cohorts of interneurons that each target specific types of pyramidal cells [80] or whether each class of interneuron provides widespread inhibition but makes stronger or more numerous connections onto certain types of projection neurons.

Activation of inhibitory circuits in the mPFC

In addition to activating projection neurons, long-range inputs engage a variety of interneurons in the mPFC. In many cases, interneurons are activated before projection neurons, thereby contributing to feedforward inhibition [41,42,73]. Once the local network is activated, feedback inhibition is also engaged, contributing to complex network dynamics [29,73,74].

PV+ interneurons across the cortex comprise two main subtypes: PV+ basket cells and PV+ chandelier cells. PV+ basket cells are found in L2 to L6 and make fast, depressing connections near the cell body of pyramidal cells (Figure 6A). By contrast, PV+ chandelier cells are prevalent at the L1/2 border and target the axon initial segment of pyramidal cells (Figure 6A). Feedforward inhibition across the cortex is primarily mediated by PV+ basket cells, which gate responses to long-range inputs and thus control signal transmission [41,42,73]. In the mPFC, cortical, thalamic, BLA, vHPC, and claustral inputs all strongly activate PV+ basket cells, albeit in different layers [41,42,56,77,82–84] (Figure 6C). While less studied, cortical inputs also engage PV+ chandelier cells, which preferentially target L2 cortico-amygdalar neurons to regulate their output [79].
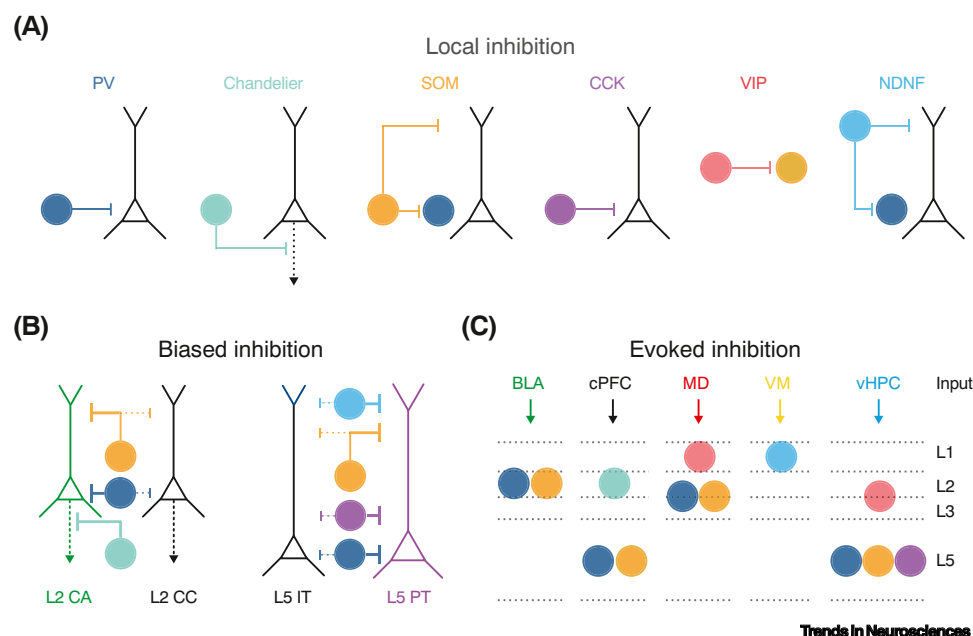
Figure 6. Inhibitory circuits in the medial prefrontal cortex (mPFC). (A) Targeting of pyramidal cells by parvalbumin (PV)+ basket cells, PV+ chandelier cells, somatostatin (SOM)+ cells, cholecystokinin (CCK)+ cells, and neuron-derived neurotrophic factor (NDNF)+ cells, along with targeting of SOM+ cells by vasoactive intestinal peptide (VIP)+ cells and PV+ cells by SOM+ cells and NDNF+ cells. (B) Biased inhibitory inputs onto neighboring projection neurons. PV+ (basket and chandelier cells) and SOM+ cells preferentially contact layer (L)2 cortico-amygdalar (CA) neurons over L2 corticocortical (CC) neurons. PV+, SOM+, CCK+, and NDNF+ preferentially contact L5 pyramidal tract (PT) cells over L5 intratelencephalic (IT) cells. (C) Summary of the currently known interneurons contacted by long-range excitatory inputs. The basolateral amygdala (BLA) activates L2 PV+ and SOM+ cells. The contralateral PFC (cPFC) innervates L2 chandelier cells, in addition to L5 PV+ and SOM+ cells. The mediodorsal thalamus (MD) engages both L3 PV+ and SOM+ cells, as well as L1 VIP+ cells. The ventromedial thalamus (VM) drives L1 NDNF+ cells. The ventral hippocampus (vHPC) activates L2/3 VIP+ cells and L5 PV+, SOM+, and CCK+ cells. Note that the distinct presynaptic release properties of inputs onto these cells mean that they also fire during different phases of activity.

The sparsity of PV+ interneurons in the mPFC suggests that other interneurons may also contribute to feedforward inhibition. Whole-brain rabies-tracing studies show that several other interneuron subtypes receive long-range inputs [10,11,23]. For example, our group recently showed that CCK+ interneurons are excited by vHPC inputs to mediate feedforward inhibition in the IL [77] (Figure 6C). These CCK+ interneurons target the soma of L5 pyramidal cells (Figure 6A) and show biased connections onto PT cells, similar to PV+ interneurons (Figure 6B). CCK+ synapses also undergo endocannabinoid-mediated presynaptic modulation via CB1 receptors. Surprisingly, this modulation is observed only at L5 IT cells [77], which represent the main target of vHPC inputs to the IL [61], suggesting that endocannabinoids may play a role in regulating specific networks in the mPFC, including vHPC-evoked inhibition.

Across the cortex, SOM+ interneurons are usually thought to mediate feedback inhibition at the dendrites of pyramidal cells [29,80]. However, cortical, thalamic, BLA, and vHPC inputs also innervate and drive SOM+ interneurons in the mPFC [10,11,41,42,77] (Figure 6C). In each case, these connections undergo pronounced facilitation, similar to local excitatory inputs from nearby pyramidal cells [41]. Equivalent targeting is also found in the sensory cortex, with gradual transition from PV- to SOM-mediated inhibition during ongoing activity [29]. Together, these findings suggest that a variety of long-range afferents can drive robust feedforward inhibition in the mPFC, which shifts from the soma to the dendrites of pyramidal cells during repeated activation.

5HT3aR+ interneurons are primarily found in superficial layers and can also contribute to feedforward inhibition [23,29]. In the sensory cortex, L1 interneurons are subdivided into NDNF+, VIP+, and alpha-7 nicotinic receptor expressing cells, with the NDNF+ cells further subdivided by the expression of neuropeptide Y (NPY+) (NDNF+/NPY+ and NDNF+/NPY–) [22]. In the mPFC, NDNF+ cells are prominent in L1a whereas VIP+ cells are absent from L1a, being instead found in L1b and L2/3 [23]. These interneurons are targeted by particular long-range inputs, with recent work from our laboratory showing that VM drives NDNF+ cells in L1a whereas MD engages VIP+ cells in L1b [23] (Figure 6C). vHPC inputs may also target VIP cells in L2/3 [85], whereas the claustrum activates a separate NPY+ population in deeper layers [84]. Importantly, L1 interneurons are also major recipients of many major neuromodulatory inputs, which are more abundant in mPFC than sensory cortex, influencing many receptors and channels to regulate interneuron function [32,86].

Last, subsets of interneurons mediate multiple forms of 'disinhibition' by selectively targeting other interneurons. As in sensory cortex, VIP+ cells target SOM+ cells, which in turn also target PV+ cells [23,87–89] (Figure 6A). Recent work shows that NDNF+ cells in L1 target PV+ cells in L2/3 in a separate disinhibitory circuit [23]. By contacting VIP+ and NDNF+ cells, long-range afferents can thus drive different disinhibitory networks involving SOM+ or PV+ cells (Figure 6C). Ultimately, the impact of a given input on the mPFC depends on the complex interplay of excitation, inhibition, and disinhibition. A goal for future work is to establish which of these responses dominates *in vivo* activity and how these different circuit motifs contribute to behaviors involving the PFC.

Functional implications of mPFC connectivity

We are beginning to understand how specific circuits in the mPFC communicate with the rest of the brain to shape high-level behaviors. One important feature of the mPFC is that long-range inputs directly target and activate specific types of projection neurons, with several reciprocally organized networks, including with cortex, thalamus, and BLA. These circuits are well placed to support the sustained, delay-period activity observed in the PFC during short-term memory tasks [14,50,51]. This organization is very different from sensory cortex, where thalamic inputs primarily engage local circuit neurons and are processed in a hierarchical manner. Additional studies are now needed to explore other long-range inputs, including excitatory connections from the ipsilateral cortex and claustrum as well as inhibitory inputs from the basal ganglia.

While long-range inputs to mPFC directly engage projection neurons, they also trigger local communication. For example, IT cells receive input from BLA (in L2), thalamus (in L3), and vHPC (in L5) before relaying information to other projection neurons [16,33]. Thus, L5 PT cells are directly activated by long-range inputs while also integrating the activity of IT cells distributed over multiple layers. Interestingly, the activity of PT cells may be coordinated via enriched thalamic input to their apical dendrites, a notable difference between mPFC and sensory cortex. This connectivity is instead reminiscent of circuits in the hippocampus, where perforant path inputs contact the apical dendrites of pyramidal cells, allowing them to gate responses to other inputs that target proximal dendrites [90]. In the future, it will be interesting to assess the functional implications of VM inputs to PT cells, including the regulation of synaptic plasticity.

The targeting of long-range inputs to different classes of interneurons also sculpts functional responses in the mPFC. By engaging distinct local inhibitory circuits, long-range inputs can have unexpected and interesting influences. For example, VM strongly engages L1 NDNF+ cells to inhibit the dendrites of PT cells, effectively silencing dendritic excitation [23]. By contrast, cPFC inputs target PV+ interneurons, controlling activity at the soma [42,56]. The activation of PV+

interneurons is reduced during ongoing activity, whereas SOM+ cells becoming increasingly engaged by repetitive stimulation [41]. Finally, vHPC inputs target CCK+ interneurons, whose presynaptic terminals are uniquely sensitive to endocannabinoid signaling [77]. Moving forward, it is important to assess the functional implications of these findings and how different forms of inhibition are regulated, including by neuromodulators that shape *in vivo* dynamics and behavior.

Last, it is important to remember that wiring rules can differ across subregions of the mPFC that play distinct roles in behavior [91,92]. For example, afferents from vHPC and BLA show graded innervation along the dorsoventral axis of the mPFC. They also display distinct laminar targeting in each subregion, with BLA and vHPC input segregating in L2 and L5 of PL but overlapping in L5 of IL. Moreover, they show varying cell-type specificity across subregions, with BLA targeting L2 cortico-amygdalar neurons in PL but L5 PT cells in IL [40,63] and vHPC targeting L5 IT cells in IL [61]. By contacting different subregions, layers, and projection neurons, each long-range input has distinct effects on the local circuit and thus has a unique impact on downstream brain regions.

Concluding remarks

Different cortical regions share many common features, including a laminar structure, excitatory and inhibitory cells, and specific wiring rules [5,34,38]. However, major regional variation also exists, with the fundamental building blocks of the cortex assembled in unique ways to enable specialized functions. Among the keys to understanding the cortex is to appreciate that these differences between regions are at least as important as the similarities. The mPFC is distinguished from primary sensory cortex in several important ways, including being agranular and displaying distinct connectivity characterized by enormous variety of both projection neurons and long-range inputs. Understanding the specific cell types, local connections, and long-range networks of the mPFC provides an important framework to assess how the properties of mPFC circuits contribute to specific functions, including how these networks integrate multiple types of task-relevant information and support delay-period activity and ultimately how specific mPFC circuit elements control behavior (see Outstanding questions) [18,50–53].

Declaration of interests

The authors declare no interests in relation to this work.

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