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The rodent medial prefrontal cortex and associated circuits in orchestrating adaptive behavior under variable demands

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Abstract

Emerging evidence implicates rodent medial prefrontal cortex (mPFC) in tasks requiring adaptation of behavior to changing information from external and internal sources. However, the computations within mPFC and subsequent outputs that determine behavior are incompletely understood. We review the involvement of mPFC subregions, and their projections to the striatum and amygdala in two broad types of tasks in rodents: 1) appetitive and aversive Pavlovian and operant conditioning tasks that engage mPFC-striatum and mPFC-amygdala circuits, and 2) foraging-based tasks that require decision making to optimize reward. We find support for region-specific function of the mPFC, with dorsal mPFC and its projections to the dorsomedial striatum supporting action control with higher cognitive demands, and ventral mPFC engagement in translating affective signals into behavior via discrete projections to the ventral striatum and amygdala. However, we also propose that defined mPFC subdivisions operate as a functional continuum rather than segregated functional units, with crosstalk that allows distinct subregion-specific inputs (e.g., internal, affective) to influence adaptive behavior supported by other subregions.

Keywords

Prelimbic; Infralimbic; Decision making; Reward; Fear; Dorsal striatum; Ventral striatum; Nucleus accumbens; Dopamine

1. Introduction

The medial prefrontal cortex (mPFC) of the rodent has been the subject of intensive study over the past 40 years, resulting in thousands of published reports describing its structure

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and function. This wealth of information has resulted in several theories of specifically what and how this brain region contributes to behavior. While broad agreement remains elusive, important clues exist regarding the role of the mPFC and its computations in generating adaptive behavior. The goal of this review is to identify general features of rodent mPFC structure and function that are necessary to understand its role in behavior by synthesizing recent literature. Our goal is *not* to propose a new unifying theory of the role of mPFC in generating adaptive behavior, but rather we suggest a framework that can be used to inform and constrain future theories.

The framework proposed herein is created from anatomical and functional data that are well validated and provide foundational principles of mPFC function. As will be discussed in greater detail, this framework highlights the existence of a functional gradient along the dorsoventral axis of mPFC that is defined by distinct, but overlapping input/output patterns, shifting away from considering traditionally defined subdivisions within the mPFC (e.g., anterior cingulate cortex, prelimbic cortex, infralimbic cortex) as being anatomically and functionally segregated. We propose that the mPFC is composed of local microcircuits that are highly recurrent, and interconnected with other local microcircuits, for feedforward inhibition or excitation of other areas along the mPFC continuum. Thus, local microcircuits are embedded within a larger macrocircuit that spans the entirety of the mPFC, and distinct inputs to one part of the mPFC (e.g., affective information arriving in the ventral mPFC) may influence activity in other areas of the mPFC (e.g., motor output mediated by dorsal mPFC). This anatomical arrangement may also enable adaptive behavior by implementing computations in a flexible manner as determined by external (environmental cues, nature of the task, past and present task demands) and internal factors (inputs to mPFC that are activated, neurotransmitters (e.g., dopamine), and plasticity). The activation of internal factors, such as interoceptive cues, likely induce the activation of distinct inputs to the mPFC, which may facilitate the activation/inhibition of different sub-areas and the computations that support a range of behaviors from the most basic to complex.

In this review, we will focus on how appetitive and aversive stimuli and their associated cues, along with specific task demands, are supported by a multitude of intermingled neural circuits in the mPFC and influence behavioral output via their recruitment of downstream targets in the striatum and amygdala (Fig. 1). We will review the literature related to mPFC neural activity that is governed by Pavlovian and operant contingencies vs. that required for decision making in some more complex tasks. By integrating the wealth of information from these diverse experimental approaches, we will develop our framework for how the mPFC processes information to determine responses that are optimized to meet the present demands of a task. Further, we discuss the general properties that guide computation in rodent mPFC and the contributions of subcircuits. This framework provides foundational principles that can be used to describe how such a wide range of behaviors is influenced by this brain region: it is largely attributable to interactions amongst a diverse array of efferents and afferents that converge in highly recurrent networks.

2. Rodent medial prefrontal cortex and associated circuitry involved in adaptive responding

The anatomy of rodent mPFC and its homology with subregions of the primate PFC has been discussed at length elsewhere (Euston et al., 2012; Hoover and Vertes, 2007; Laubach et al., 2018; Uylings et al., 2003). In the present paper, we use the conventions developed by Euston, Laubach, and their colleagues in recent reviews (Euston et al., 2012; Laubach et al., 2018). Briefly, the rodent mPFC can be subdivided into a dorsal aspect (dmPFC) encompassing the dorsal prelimbic (dPL) and the anterior cingulate cortex (ACC) and a ventral aspect (vmPFC) that encompasses the ventral PL, the infralimbic cortex (IL) and the dorsal peduncular cortex (DP). Anatomical features of importance are that glutamatergic connections within each mPFC subregion are highly recurrent, and that the mPFC subregions are interconnected via glutamatergic and GABAergic projections, enabling crosstalk between them (Anastasiades and Carter, 2021). The PL and ACC, and PL and IL have strong reciprocal connectivity, while the connection between the ACC and IL is somewhat biased with greater directionality of inputs from IL to ACC (Hoover and Vertes, 2007; Jones et al., 2005; Vertes, 2004). This connectivity suggests that affective/interoceptive information processed by the vmPFC can influence dmPFC outputs. Studies investigating interactions between different mPFC subdivisions are sparse, but in one slice electrophysiology study, van Aerde et al. (2008) induced fast network oscillations in the PL and IL with the application of muscarinic agonist carbachol, and found that the IL oscillated at higher power and frequencies than in the PL. Intriguingly, they also established that the differential oscillatory activity is a product of interaction between the PL and IL, as the difference disappeared when the two areas were disconnected. They also observed that the power of PL and IL fast network oscillations was reduced in connected, compared to isolated slices, hence indicating that the interactions between the PL and IL can be inhibitory.

The entire mPFC receives diverse inputs from motor, sensory, affective, and visceral areas of the brain, but connectivity patterns also differ along the dorsoventral aspects of the mPFC (Euston et al., 2012; Hoover and Vertes, 2007; Vertes, 2004). Both the dmPFC and vmPFC receive strong dopaminergic input from the VTA (Swanson, 1982). The dmPFC receives prominent cortical projections from sensory, somatosensory, and motor regions, but weaker projections from limbic areas (Carr and Sesack, 2000; Hoover and Vertes, 2007; Levesque and Parent, 1998). In contrast, the vmPFC, and specifically the IL is completely devoid of cortical afferents from motor, sensory and sensorimotor areas (Hoover and Vertes, 2007) but receives dense limbic input from the hippocampal formation and amygdala, as well as visceral input from the posterior insular cortex (Hoover and Vertes, 2007). Together, inputs to the mPFC may convey information regarding the motivational salience and value of internal and external stimuli.

The entire mPFC can exert control over action selection and execution via its projections to areas such as the amygdala, nucleus accumbens, and associated motor output structures such as the dorsal striatum and the ventral pallidum (Gabbott et al., 2005; Hoover and Vertes, 2007). However, the output patterns of the dmPFC and vmPFC also differ based

on their specialized roles in cognitive/response control and affective/visceromotor functions, respectively (Euston et al., 2012). In general, the dmPFC projects to motor and premotor areas while the vmPFC preferentially projects to autonomic and limbic centers (Gabbott et al., 2005; Vertes, 2004). As a more specific example of this principle, the rodent mPFC provides direct, topographically organized output to the striatum (Berendse et al., 1992; Voorn et al., 2004), forming multiple segregated loops which may compute dissociable types of responding in behavioral tasks (Floresco, 2015). DmPFC inputs to the dorsal striatum are strongest in the medial compartment, whereas the dorsolateral striatum receives inputs from sensorimotor regions of cortex (Hunnicutt et al., 2016; Peters et al., 2021). This topographic organization allows cortico-striatal circuits to exert differential control over behavior, with the dmPFC-dorsomedial striatum circuit supporting goal-directed behaviors guided by outcome value (Corbit et al., 2012; Peak et al., 2020), and the sensorimotor-dorsolateral striatum circuit mediating well-learned behaviors that become stimulus driven, often referred to as habitual (O'Hare et al., 2016; Yin et al., 2004). Regarding the ventral striatum, the dmPFC (PL subregion) sends a projection to the nucleus accumbens core, a circuit thought to be involved in goal directed behavior particularly in the appetitive domain (Berendse et al., 1992; Hoover and Vertes, 2007). In contrast, the vmPFC (IL subregion) projects preferentially to the nucleus accumbens shell subregion (Berendse et al., 1992), a circuit involved in more procedural or habit responding (Barker et al., 2014).

In sum, the anatomical organization of the mPFC is optimally suited for a structure involved in forming plans to achieve goals, as highly processed inputs, and information regarding motivational value, can be readily linked to the early stages of motor output.

3. mPFC in adaptive responses to motivationally significant signals

Adapting to dynamic environments requires the ability to successfully appraise interoceptive and external cues, as well as different outcome contingencies to effectively orchestrate approach and avoidance behaviors. As discussed in Section 2, the mPFC is well positioned to subserve the evaluation and integration of motivationally significant events, and to co-ordinate the execution of an appropriate behavioral response. This function is also reflected in neural activity in the mPFC during a variety of task events in both aversive and appetitive preparations. Cells in the mPFC are highly responsive to the anticipatory period preceding outcome delivery, to cues that signal both appetitive and aversive outcomes, and to the delivery of the outcomes themselves (Baeg et al., 2001; Chang et al., 1997; Gentry and Roesch, 2018; Gilmartin and McEchron, 2005; Pratt and Mizumori, 2001). In this section, we will discuss experimental evidence that the mPFC plays an integral role in monitoring current task demands as determined by the changing availability of cues signaling reward and punishment and guiding when and how to respond.

3.1. Challenging the dichotomous function of the PL and IL in the expression and extinction of conditioned fear and reward-seeking

The PL and IL subregions of the mPFC are thought to play functionally dichotomous roles in mediating conditioned responding to appetitive and aversive cues and outcomes. While the PL is implicated in the formation and expression of conditioned responding the

IL is thought to be involved in the inhibition and extinction of conditioned responding when an anticipated outcome is omitted (Gourley and Taylor, 2016; Peters et al., 2009; Quirk and Mueller, 2008). This proposed dichotomy of PL/IL function largely stems from research in aversive conditioning, but has also been observed in appetitive conditioning procedures, particularly in models of substance use disorders. However, emerging evidence has challenged this dichotomy and suggests that the PL and IL may instead work in concert to control responding to appetitive and aversive stimuli.

In aversive preparations, PL activity is modulated by aversive outcomes (shock) and cues that signal the aversive outcome and correlates with the degree of conditioned responding to the aversive cue (Burgos-Robles et al., 2009; Fitzgerald et al., 2014; Gilmartin and McEchron, 2005). In contrast, IL activity decreases in response to an aversive outcome (Gilmartin and McEchron, 2005), and is instead correlated with the extinction and inhibition of conditioned responding to aversive cues (Gilmartin and McEchron, 2005; Giustino et al., 2016; Milad and Quirk, 2002). Pharmacological inactivation of the PL suppresses conditioned responding to aversive cues (Laurent and Westbrook, 2009; Sierra-Mercado et al., 2011), and abolishes the acquisition and retrieval of conditioned place avoidance to different noxious stimuli (Jiang et al., 2014). Conversely, disrupting IL activity leaves aversive conditioning intact but has consistently been shown to impair extinction learning, in which animals learn to inhibit conditioned responses when the aversive outcome is withheld (Do-Monte et al., 2015a; Lay et al., 2020; Lebron et al., 2004; Morgan et al., 2003; Quirk et al., 2000; Sierra-Mercado et al., 2006). Furthermore, enhancing IL activity has reliably been shown to suppress aversive conditioned responding and to facilitate extinction learning (Do-Monte et al., 2015a; Kim et al., 2010; Lingawi et al., 2018, 2017; Milad and Quirk, 2002; Milad et al., 2004; Peters et al., 2010; Thompson et al., 2010; Vidal-Gonzalez et al., 2006), whereas augmenting PL activity has been shown to be disruptive or have no effect on extinction (Thompson et al., 2010; Vidal-Gonzalez et al., 2006). Lastly, presenting an aversive cue in the context in which it was extinguished results in greater activation of the IL, whereas presenting the cue in a different context triggers a return of responding and greater activation in the PL (Knapska and Maren, 2009). Thus, substantial evidence from aversive conditioning studies supports the dichotomy between the PL in expression and the IL in inhibition of a conditioned fear response. However, it is important to note that the PL and IL are interconnected regions, and their combined activity may be necessary to effectively initiate the appropriate response in aversive tasks. For instance, recent work has shown that optogenetic activation of a PL-IL circuit can facilitate extinction acquisition and extinction retrieval of conditioned fear (Marek et al., 2018). Therefore, the PL may also play a role in extinction, and the functional dichotomy between the PL and IL in expression and inhibition of conditioned fear is not always as clear-cut.

The dichotomous functions of the PL and IL in cued reward-seeking have also been widely observed within the framework of substance use disorder (Peters et al., 2009). Early studies found that lesions of the PL disrupt acquisition of cocaine conditioned place preference (Isaac et al., 1989; Tzschentke and Schmidt, 1998), and retrieval of cocaine conditioned place preference engages GABAergic cells in the PL, but not the IL (Miller and Marshall, 2004). In contrast, disrupting IL activity after extinction can disinhibit and trigger a robust return of otherwise extinguished cocaine- and heroin-seeking (Ovari and Leri, 2008; Peters

et al., 2008). Additionally, optogenetic inhibition of the IL during extinction of cocaine-seeking can impair extinction acquisition and subsequent retrieval (Gutman et al., 2017b; Van den Oever et al., 2013). Thus, the PL and IL appear to have opposite roles in the expression and extinction of drug-seeking. However, pharmacological inactivation of the PL and IL have also been shown to have similar effects in reducing responding to an alcohol-cue (Khoo et al., 2019). Interestingly, this effect was only observed under extinction conditions in which alcohol was omitted, and not when alcohol was present (Khoo et al., 2019). These results suggest that the PL and IL may sometimes work in concert to control responding to different drugs of abuse.

The contrasting roles of the PL and IL in generating and inhibiting conditioned reward-seeking have also been corroborated in reinstatement models, in which extinguished drug-seeking returns after reexposure to the drug or drug-associated cues and context. PL activation correlates with the reinstatement of cocaine- and heroin-seeking (James et al., 2018; McGlinchey et al., 2016; Rubio et al., 2019). Furthermore, pharmacological inactivation of the PL, but not the IL attenuates return of cocaine-seeking after extinction that is triggered either by exposure to cocaine, cocaine-associated cues, or stress (foot--shock) (Capriles et al., 2003; Fuchs et al., 2005; McFarland and Kalivas, 2001; McLaughlin and See, 2003). In contrast, enhancing IL activity reduces the reinstatement of responding for cocaine, heroin, and alcohol (Augur et al., 2016; Chen et al., 2016; Gass et al., 2014; LaLumiere et al., 2012). However, inconsistent findings have also shown that pharmacological inactivation of the IL does not affect the return of alcohol-seeking (Pfarr et al., 2015; Willcocks and McNally, 2013), and can even reduce reinstatement of heroin-seeking after extinction (Bossert et al., 2011; Bossert et al., 2012; Rogers et al., 2008). These findings suggest that the IL does not indiscriminately inhibit drug-seeking across different drug reinforcers but may sometimes play a similar role as the PL in reinstatement. Crosstalk between the PL and IL may be imperative for determining whether to respond or withhold responding during reinstatement.

Studies investigating the role of the PL and IL in mediating responding to natural reinforcers such as food or sucrose have yielded mixed findings across different tasks. Consistent with the proposed dichotomy, blocking dopaminergic transmission in the PL abolished acquisition, while elevating dopamine transmission in the IL attenuated acquisition of sucrose conditioned place preference (Hayen et al., 2014). Moreover, PL inactivation has been shown to attenuate the reinstatement of operant responding for sucrose (Eddy et al., 2016; Trask et al., 2017). However, reinforced operant responding for food is not impacted by PL inactivation per se (Ball and Slane, 2012; Calu et al., 2013). In contrast, lesions of the IL enhance the cue-elicited reinstatement of Pavlovian food-seeking after extinction (Rhodes and Killcross, 2007a,b, 2004). Furthermore, pharmacological and optogenetic activation of the IL can suppress the return of Pavlovian responses to a sucrose cue following extinction (Villaruel et al., 2018). Interestingly, IL inactivation also disinhibits operant responding in the extinction context, highlighting an important role for the IL in contextual control of conditioned behaviors (Eddy et al., 2016; Laurent et al., 2016). Inconsistently, however, IL inactivation has also been shown to have no effect on initial extinction of operant responding for sucrose or food (Caballero et al., 2019; Mendoza et al., 2015; Warren et al., 2016) and reduces reinstatement of food- and sucrose-seeking (Caballero et al., 2019; Eddy et al.,

2016). Furthermore, pharmacological inactivation of the IL can even facilitate extinction of conditioned responding to a food and sucrose cue (Lay et al., 2019; Mendoza et al., 2015). These studies contradict the proposed dichotomy between the PL and IL, indicating that the two subregions may play similar roles in controlling conditioned responding.

3.2. Coordinated PL and IL function is necessary for discriminative cue control over instrumental behavior

Empirical support for the proposed dichotomous roles of the PL and IL in conditioned reward-seeking and fear diminishes further when we consider studies that have examined the role of the PL/IL in tasks that require higher order processing of cue-outcome contingencies. For example, PL and IL appear to be equally recruited when animals are required to monitor and adaptively respond to changing cue contingencies. Electrophysiological recordings from the PL and IL of rats performing discriminative responding for appetitive and aversive cues in the same testing session showed that neural activity in the PL and IL are more attuned to cues predictive of appetitive outcomes, relative to cues that predict aversive or no outcomes (Gentry and Roesch, 2018). Furthermore, in a study that compared the role of the PL and IL in mediating Pavlovian responses to discriminative cues signaling reward, fear, and safety in one task, PL and IL inactivation led to diminished anticipatory nosepoke responses to the reward cue, reduced freezing to the fear cue, and attenuated the ability to discriminate between cues (Sangha et al., 2014). The necessity of both the PL and IL is also apparent under conditions in which instrumental responding is under the control of discriminative cues signaling reward vs. non-reward. Inactivation of the PL or the IL consistently results in diminished reinforced responding in the presence of a cue that signals reward (sucrose or cocaine), along with increased responding to a cue that signals no reward (Di Pietro et al., 2006; Ghazizadeh et al., 2012; Gutman et al., 2017a; Ishikawa et al., 2008a,b). In these studies, however, responses were reinforced, thus permitting within-session feedback to guide subsequent responding even in the absence of previously learned cue-outcome associations. Moorman and Aston-Jones (Moorman and Aston-Jones, 2015) studied the role of the mPFC in discriminative cue responding under reinforced and non-reinforced conditions (i.e., in extinction), and found that both PL and IL were necessary for cue-elicited sucrose-seeking under extinction conditions, but only the IL was critical in supporting reinforced cue-elicited reward-seeking. Furthermore, PL and IL recruitment has been shown to be required in mediating contextual control over adaptive, discriminative responding. Electrophysiological recordings revealed that neuronal activity in both PL and IL encode contextually appropriate cued reward-seeking under non-extinction conditions, and withholding of responses during extinction (Gentry and Roesch, 2018; Moorman and Aston-Jones, 2015). These findings are in accord with lesion and pharmacological studies showing that contextual control over discriminative cue responding for reward is impacted by PL or IL inactivation both under reinforced, and extinction conditions (Ashwell and Ito, 2014; Riaz et al., 2019). The PL and IL are also recruited in the use of contextual cues to disambiguate between conflicting cue-outcome contingencies under extinction and guiding instrumental responding for food (Eddy et al., 2016; Haddon and Killcross, 2005; Laurent et al., 2016; Marquis et al., 2007). Taken together, these findings suggest that the PL and IL act cooperatively to detect and disambiguate multiple cues in the environment (context/discrete

cue/valence), to enable the deployment of the most appropriate behavioral response in a given situation.

Studies investigating the role of the mPFC in instrumental responding motivated by single, or multiple aversive cues suggest a more nuanced role for the IL and PL. When animals are exposed to a single cue signaling the impending delivery of an aversive outcome, IL, but not PL inactivation impairs the ability of the warning cue to evoke a shuttle response, or a lever press to avoid the outcome (i.e., active avoidance; Capuzzo and Floresco, 2020; Moscarello and LeDoux, 2013). However, when a discriminative component is introduced, such that animals are required to discriminate between a warning cue (active avoidance), and an inhibitory cue during which an emission of a lever press leads to shock delivery (inhibitory avoidance), IL inactivation impairs both active and inhibitory avoidance, but PL inactivation selectively disrupts active avoidance (Bravo-Rivera et al., 2014; Capuzzo and Floresco, 2020; Diehl et al., 2018).

Emerging evidence have found separate neuronal ensembles within the mPFC that are involved in the generation and suppression of conditioned responding, which could explain the discrepancies found in the literature following manipulations of the entire PL or IL cortices (Bossert et al., 2011; Laque et al., 2019; Pfarr et al., 2015, 2018; Suto et al., 2016; Warren et al., 2019, 2016). Specifically, separate neuronal ensembles in the IL are activated following the expression or extinction of cocaine-seeking (Warren et al., 2016). Selective ablation of neurons in the IL that are activated during expression decreases cocaine-seeking but ablation of neurons that are activated during extinction increases cocaine-seeking (Warren et al., 2016). Furthermore, in a discriminative instrumental conditioning procedure, selective ablation of neuronal ensembles in the IL that are activated by a reward-predictive cue decreases reward-seeking specifically to that cue (Suto et al., 2016). In contrast, selective deletion of neuronal ensembles in the IL that are activated by a cue predicting the absence of reward, increases reward-seeking specifically to that cue (Suto et al., 2016). Therefore, the IL alone seems capable of tracking changing contingencies between stimuli, actions, and outcomes either after extinction or through discriminative stimuli. Future studies could investigate the interaction of these neuronal ensembles within and across different subregions of the mPFC to delineate how the mPFC may integrate different task demands to orchestrate the appropriate response.

3.3. mPFC-nucleus accumbens circuits in mediating expression and inhibition of reward-seeking

How might the PL and IL co-ordinate the emission of behaviorally appropriate responses in a changing environment? Glutamatergic projections from the mPFC to the nucleus accumbens may serve as one critical portal through which adaptive responses are selected, and competing responses suppressed. As mentioned in Section 2, corticostriatal projections are topographically organized, with the dorsal aspects of the mPFC and the PL in particular, preferentially projecting to the nucleus accumbens core (NAcC), and the more ventral aspects/IL projecting to the nucleus accumbens shell (NAcS) (Berendse et al., 1992; Voorn et al., 2004). Furthermore, the functional dichotomy between the PL and IL is thought to be maintained in these largely segregated projections, with the PL-to-NAcC being involved

in expression and the IL-to-NAcS being involved in inhibition of reward-seeking behaviors (Peters et al., 2009).

Much of the evidence for the PL-NAcC circuit supporting reward-seeking is derived from studies using drug-reinstatement models. Inactivation of the PL has been shown to block cocaine-, heroin, or stress-induced glutamate release in the NAcC, while diminishing reinstatement of drug-seeking (LaLumiere and Kalivas, 2008; McFarland et al., 2004, 2003). Optogenetic inhibition of the PL, NAc or PL-NAcC pathway also diminishes cocaine or cue-elicited reinstatement of cocaine-seeking (Stefanik et al., 2016, 2013). Additionally, the PL-NAcC pathway has been shown to be recruited during cue-induced reinstatement of cocaine-seeking, and disruption of communication in this pathway via pharmacological disconnection attenuates cued reinstatement of responding (James et al., 2018; McGlinchey et al., 2016). Interestingly, disconnecting the PL-NAcC circuit does not impact cued reinstatement of sucrose-seeking, bringing into question the generalizability of the proposed role of the PL-NAcC in initiating drug-seeking to natural reward-seeking. However, in a study by Ishikawa et al. (2008a,b), pharmacological inactivation of the PL was found to abolish firing in the NAcC during sucrose-seeking under the control of a discriminative stimulus. Furthermore, optogenetic activation of PL inputs to the NAc has been shown to enhance acquisition of conditioned sucrose-seeking while inhibition reduces conditioned sucrose-seeking (Otis et al., 2017). Thus, while there is extensive evidence substantiating the necessity of PL-NAcC pathway activation in the expression of relapse to drugs of abuse, further studies are also needed to establish the role of this pathway in natural reward-seeking.

Conversely, concurrent pharmacological inactivation of IL and the NAcS has been shown to disinhibit extinguished responding for cocaine (Peters et al., 2008). Further, enhancing glutamatergic activity in the IL suppresses cue-induced cocaine-seeking but is reversed by dopamine administration in the NAcS (LaLumiere et al., 2012). Neuronal ensembles in the IL that are activated during extinction are also found to predominantly project to the NAcS, and disconnecting this projection leads to an increase in cocaine-seeking (Warren et al., 2019). Divergent findings, however, have been observed in heroin self-administration procedures, in which IL-to-NAcS inactivation and disconnection instead leads to a reduction of heroin-seeking after extinction (Bossert et al., 2012). Thus, the role of the IL-NAcS circuit in extinction and inhibition may not be universal across different drug reinforcers.

Enhancing IL-NAcS circuit activity is thought to attenuate responding by promoting extinction retrieval (Augur et al., 2016; Peters et al., 2009). Consistently, optogenetic activation of the IL-NAcS circuit can also suppress context-induced renewal of responding to a sucrose-predictive cue after extinction (Villaruel et al., 2021). Further, chemogenetic activation of the IL-NAcS circuit has been shown to attenuate cue-induced cocaine-seeking only after extinction training (Augur et al., 2016). Activation of the IL-NAcS circuit, however, has also been shown to reduce cocaine-seeking after abstinence and without prior extinction training (Cameron et al., 2019). Further, optogenetic activation of the IL-NAcS circuit during presentations of a sucrose-predictive cue can inhibit responding even without prior extinction training (Villaruel et al., 2021). Lastly, cocaine self-administration and incubation of cocaine craving can alter glutamatergic transmission in the IL-NAcS circuit

independent of extinction (Cameron et al., 2019; Ma et al., 2014; Pascoli et al., 2014). Therefore, it is unclear whether IL-NAcS circuit activation suppresses responding through an extinction process. The inhibitory role of the IL-NAcS circuit in appetitive behaviors may instead be part of a broader function of coordinating responding when multiple cue and outcome contingencies are present. Pharmacological inactivation of the IL alters neural activity in the NAcS which increases responding to cues that signal no reward (Ghazizadeh et al., 2012). Interestingly, concurrent augmentation of glutamatergic transmission in the IL and dopaminergic transmission in the NAcS also increases responding to an inactive lever which has no programmed consequence in a cocaine-seeking task (LaLumiere et al., 2012). Similar disinhibitory effects have also been observed following IL-NAcS disconnection which further impairs the ability to use cues to guide operant responding in a task that requires discriminating between different cue and outcome contingencies (Keistler et al., 2015). Therefore, the IL-NAcS circuit may be important for suppressing responding to irrelevant cues and competing actions to better coordinate effective responding under variable task demands.

3.4. mPFC-amygdala circuits in expression and inhibition of conditioned fear

While the role of mPFC-NAc circuits in coordinating adaptive responding in the context of reward-seeking is well established, the absence of studies investigating the role of mPFC-NAc circuits in the expression and inhibition of conditioned avoidance and fear is noticeable in the literature. Instead, there is strong evidence that the PL and IL may recruit downstream amygdala targets to exert differential control over fear-related behavior (Arruda-Carvalho and Clem, 2015). Support exists for the role of the PL-BLA pathway in the acquisition and expression of conditioned fear (Arruda-Carvalho and Clem, 2014), although the engagement of the pathway appears to be time-dependent, with optogenetic inhibition of the PL-BLA pathway affecting conditioned fear expression at 6hrs, but not at 7 days after fear conditioning (Do-Monte et al., 2015b). In contrast, the IL is thought to promote extinction by activating inhibitory intercalated neurons in the amygdala, which in turn inhibits the output of the central amygdala (CeA) (Berretta et al., 2005; Quirk et al., 2003). Fear extinction also alters synaptic properties of the IL-BLA pathway (Bloodgood et al., 2018; Cho et al., 2013; Strobel et al., 2015), and inactivation of the IL-BLA pathway during extinction impairs extinction retrieval the following day (Bloodgood et al., 2018; Bukalo et al., 2015). Together, there is evidence suggesting that the mPFC-amygdala circuit is important for mediating fear-related behaviors. However, it should be noted that as with the apparent lack of studies showing mPFC-NAc involvement in fear-related processes, there is also a paucity of studies investigating the role of the PL/IL-amygdala circuits in conditioned reward-seeking. Thus, future studies need to be directed at investigating the role of the mPFC-amygdala circuit in appetitive-related tasks given the amygdala's role in reward processing (Baxter and Murray, 2002).

3.5. Conclusions

In summary, while there is evidence for the PL and IL subserving dichotomous, and sometimes opposing functions in the expression and inhibition of conditioned fear and cued reward-seeking, it is also abundantly clear that co-recruitment of the PL and IL occurs in certain situations that call for higher order discrimination and disambiguation

of multiple environmental cues that signal availability/non availability of food and threat/safety for adaptive responding. The PL and IL are highly interconnected via recurrent excitatory projections, and their microcircuit organization may allow for their interaction to be opposing (via feed forward activation of GABAergic interneurons) or cooperative (via feedforward pyramidal cell activation), as task demands dictate. We propose that neuronal ensembles exist in the PL and IL that receive distinct inputs from the limbic system (e.g., hippocampus, amygdala, orbitofrontal cortex), which convey highly processed motivationally significant information pertaining to cues, context, valence, as well as outcomes. Although not directly discussed in the review, the dopaminergic innervation of the mPFC likely attributes salience to specific inputs to the mPFC (e.g., Hayen et al., 2014), leading to the activation of select neuronal ensembles, and potentially inhibition of 'competing' ensembles through recurrent feedforward inhibition of neighboring ensembles (Anastasiades and Carter, 2021). Communication between ensembles and between the IL and PL may integrate incoming information from various inputs to devise a strategy and implement the optimal course of action. Subsequently, the activation of specific ensembles will excite downstream targets such as the NAc and amygdala to enable the selection and execution of a particular behavioral program (freezing, operant responses), and suppression of inappropriate programs.

4. Decision making and responding in complex tasks

While there is clear dissociation between the mPFC microcircuits that support various discrete aspects of behavior as outlined in Section 3, it is critical to consider how these circuits may interact to support complex behaviors. As mentioned previously, a fundamental feature of the mPFC is that this structure is highly recurrent, which leads to a structure that is optimally suited to coordinate several concurrent aspects of motivated behavior. To better understand how these interactions might lead to emergent properties required for the control of behavior we will discuss how populations of neurons in mPFC encode complex behaviors such as decision-making and strategies.

It is now a common approach to use dimensionality reduction techniques to characterize the temporal evolution of firing across a population of neurons (Cunningham and Yu, 2014). With this approach, trajectories can be observed that provide an intuitive description of how firing across a neural population progresses through time. The features of the trajectory (e.g., speed, path) can be remarkably stable when decisions are repeated over trials (Churchland et al., 2012; Mante et al., 2013; Sussillo, 2014). This is thought to provide a robust coding mechanism as the pattern of firing can be quite noisy trial to trial when viewed at the single neuron level (Churchland et al., 2012; Durstewitz et al., 2010). Furthermore, different paths of the neural trajectory are observed that correspond to different choices (Durstewitz et al., 2010; Kurikawa et al., 2018; Mante et al., 2013).

While decision-making can be viewed as a trajectory, strategies to guide decision-making are implemented in the parameters of the system that guide and constrain neural activity. By analogy, if the decision-making process is a train, strategies are the tracks and landscape on which it travels. More specifically, the variables that influence neural activity such as connections between neurons, noise, and time constants of neural activity provide the

scaffolding on which neural activity unfolds and, in this way, can bias the trajectory towards some pre-determined location (e.g., an action).

Determining how the brain flexibly optimizes strategies is critical to understand decision-making. It is common for agents to employ strategies that may not rely solely on the moment-to-moment value of the outcome but rather maximize reinforcement over the long term (Sutton and Barto, 2018). The use of strategies can bias for actions that lead to a desired outcome and minimize the need for repeatedly evaluating the available options *de novo*. In this way using a strategy where a response is planned in advance is adaptive as it would lead to faster, more advantageous decisions when the environment is predictable (Bissonette and Roesch, 2017; Kurth-Nelson et al., 2012; Linsenbardt et al., 2017).

When using a prospective decision-making strategy, the decision is made early, and a plan of action is formed to guide choosing the selected option. Conversely, using a reactive decision-making strategy, decisions are made in close proximity to the choice and the allocation of cognitive resources is stimulus-evoked (Braver, 2012; Kesner, 1989). Reactive choices are characterized by deliberation close in time to the choice, which can be observed in the behavior of the agent as equivocation between options immediately before choosing. The neural mechanisms employed by the brain to move between prospective and reactive strategies reflects high-level cognitive control processes, which are beginning to be illuminated (Brockett et al., 2020; Brockett and Roesch, 2021; Chen et al., 2010).

Similar to reactive and proactive processes described above, behavioral tasks have been developed to assess how animals flexibly implement retrospective and prospective strategies to guide decision-making. Memory guided foraging tasks with a spatial component engage prefrontal- and hippocampal-dependent processes to guide decision-making during foraging. The win-shift task on the radial arm maze is one such example (Floresco et al., 1997). In the win-shift task, rats receive information about where food will be located on a test trial while they perform an initial sample trial. To complete this task efficiently, the animal must use a blend of retrospective and prospective information to enable optimal performance during the test trial. Specifically, the animal must recall where reward was obtained in the past and use this information to decide on where to find reward in the future.

Several permutations of the radial arm maze have been developed to assess retrospective- or prospective-coding more directly. For example, random foraging tasks without delays, do not require rats to use a prospective strategy, and thus lead to responding that relies heavily on retrospection (Floresco et al., 1997). However, tasks that use a delay can be adapted to engage retrospective or prospective processes. It is known that the interpolation of a delay lead to the maximal number of errors when it was given in the middle of the test set (Churchwell and Kesner, 2011; Cook et al., 1985; Ferbinteanu and Shapiro, 2003; Goto and Grace, 2008; Kesner, 1989). Fewer errors are observed if the delay is early or late in the sequence as rats can use strategies to economically minimize the need to store information in working memory. More specifically, if the delay is instantiated early in the set an animal can remember the few locations where it was reinforced previously, therefore optimizing retrospective processes leading to fewer errors. However, when the delay is instantiated late

in the set, animals use prospective strategies to remember where to go next, which also leads to reductions in errors relative to when the delay is in the middle of the set.

In addition, delayed tasks without a spatial component, such as the odor span task (OST), require rats or mice to forage and sample stimuli without information to prospectively guide behavior (Dudchenko et al., 2000; Young et al., 2007). Behavioral tasks, such as delay discounting, that measure cognitive impulsivity have been crucial to determine how prospectively forming intentions of actions is implemented in the brain to guide decision-making. Delay discounting is robustly influenced by prospection, and impulsivity has even been conceptualized as the "… tendency to act without foresight" (Dalley et al., 2011). Importantly, the use of a prospective strategy reduces impulsive choices and reduces the time to reach a decision in the task (Linsenbardt et al., 2017).

4.1. The role of the mPFC in decision making and responding in complex environments

Decision-making is a brain-wide phenomena (Balleine and Dickinson, 1998; Gold and Shadlen, 2007). However, there is a well-established literature that describes the critical role of the dmPFC (including the ACC and PL) of the rodent to "prospectively organize ongoing actions" (Gisquet-Verrier and Delatour, 2006), see also (Floresco et al., 1997; Goto and Grace, 2008; Kesner, 1989; Myroshnychenko et al., 2017). Therefore, it is critical to define the computational properties of the dmPFC that facilitate the prospective control of decision-making.

Using awake, behaving neural recordings, patterns of neural activity have been observed that prospectively encode upcoming behaviors. In PFC, neural correlates of decisions to initiate actions are observable prior to their initiation indicating the intent to perform some action (Andersen and Cui, 2009; Boulay et al., 2016; Momennejad and Haynes, 2013; Sakagami and Niki, 1994; Sakagami and Tsutsui, 1999; Tanji and Hoshi, 2001). Patterns of neural activity in dmPFC that occur prior to a behavior (e.g., foraging, lever-pressing) are critical for optimal performance of a task (De Falco et al., 2019; Linsenbardt et al., 2019; Myroshnychenko et al., 2017). In addition, several studies find patterns of neural activity that predict upcoming actions prior to their initiation indicating the intent to perform them (Andersen and Cui, 2009; Boulay et al., 2016; Momennejad and Haynes, 2013; Sakagami and Niki, 1994; Sakagami and Tsutsui, 1999; Tanji and Hoshi, 2001). These studies lay the groundwork to determine, specifically, how prospective information is encoded in the brain and suggests a key role for the dmPFC.

Neural activity patterns that encode prospective information are not limited to the dmPFC but also observed in the hippocampus. Rat hippocampal place cells fire in a pattern that reflects the exploration of possible paths to forage for food (Catanese et al., 2014; Ferbinteanu and Shapiro, 2003; Itskov et al., 2008; Pfeiffer and Foster, 2013; Redish, 2016). Similarly, neurons in the rat mPFC also represent future foraging paths (Ito et al., 2015) suggesting that prospective coding of spatial locations is synergistically maintained across both regions (Schmidt et al., 2019). These data suggest a critical role for the hippocampus and dmPFC in prospectively guiding behavior.

Anatomical data indicate the involvement of distinct brain regions associated with the different behavioral strategies used to solve the radial arm task. Lesions of the hippocampus reduce performance of tasks designed to tax retrospective-guided foraging, while tasks that stress prospection are impaired following medial prefrontal and hippocampal lesions (Goto and Grace, 2008). This highlights the ability of animals to flexibly engage neural circuits in a manner that is optimized to meet the current cognitive demands of the task.

As mentioned in Section 4, the OST is one example of a task that does not require rodents to use a prospective strategy to optimize success. As the odor span task (OST) is an incrementing delayed non-matching to sample paradigm whereby rats are exposed to cups of scented sand on a platform (Dudchenko et al., 2000), the rat's most effective strategy is to search the cups for the single novel odor (for that session) to receive a reward. By moving the cups on each trial, spatial aspects of the task are minimized (although see (Dudchenko et al., 2000) for a spatial span task that does not involve odors). Given the increasing number of stimuli available during the task and its dependence of performance on the delay between trials of a given session (Murray et al., 2017), the OST is proposed to assess the capacity of short-term or working memory in rodents (Dudchenko, 2004; Dudchenko et al., 2013). Familiar odors incorrectly chosen during error trials are most frequently in the middle of the sequence, a characteristic reminiscent of some aspects of serial position effects observed in other short-term memory tasks (Scott et al., 2020).

Temporary inactivation of discrete areas in cortico-striatal-limbic circuits including the mPFC (PL; Davies et al., 2017, 2013b; Scott et al., 2020), dorsomedial striatum (Davies et al., 2017), and mediodorsal thalamus (Scott et al., 2020) impair span. Notably, however, OST performance in rats is not affected by excitotoxic lesions of the hippocampus produced after task acquisition (Dudchenko et al., 2000) or temporary inactivation of the posterior parietal cortex (Scott et al., 2018). The lack of hippocampal involvement in the OST in rats contrasts findings in humans, which show impairments in an odor span task with hippocampal lesions (Levy et al., 2003). In addition, hippocampal lesions in rats impair a spatial span task (Dudchenko et al., 2000), suggesting that the modality of the stimuli may be critical for engaging hippocampal networks in rats.

The involvement of mPFC in the OST has been the subject of additional investigation. Activity of AMPA receptors in the mPFC is necessary for task performance (Davies et al., 2013a). Using a disconnection design with reversible inactivations, the glutamatergic projections from mPFC to the dorsomedial striatum were also shown to be critical for task performance (Davies et al., 2017). Interestingly, the glutamatergic output of the mPFC appears to activate a population of GluN2B-containing NMDA receptors in the dorsomedial striatum during span as infusions of the GluN2B-containing NMDA receptor antagonist Ro25–6981 into the dorsomedial striatum impair the OST (Davies et al., 2017). These findings are consistent with additional studies showing that GluN2B-containing NMDA receptor overexpression in the forebrain (Cui et al., 2011) or systemic administration of the GluN2B-containing NMDA receptors antagonist Ro25–6981 (Davies et al., 2013a) improve and impair performance of the OST, respectively.

Given the role of the mPFC in the OST, and other working memory tasks requiring foraging, we conducted single unit recordings of PL neural activity while rats performed the OST to gain insight into the computations performed during the task (De Falco et al., 2019). Recordings were conducted during OST sessions in well-trained animals, which allowed for comparisons of neural activity patterns to the typically variable performance rats exhibit on the task to be made (Davies et al., 2013a; De Falco et al., 2019; Dudchenko et al., 2000). Neurons were further divided into putative interneurons (16% of 385 neurons) and putative pyramidal neurons (84% of 385 neurons). Analyses of the firing rates of these neurons during all sessions revealed that putative interneurons dramatically increased their firing during the transition from the delay period to foraging period when the rats were actively exploring the scented cups available on a given trial. A population of putative pyramidal neurons had their activity dynamically regulated during the delay, with a steady increase in firing during the delay accounting for considerable variance in a PCA. When the sessions were split into high and low spans, we found that increased activity during the delay period in putative pyramidal neurons, but not putative interneurons, predicted better performance on that task.

When the approach to the stimuli during the task were considered, the neural trajectories of putative pyramidal neurons were altered significantly more around the time of novel odor approach, when compared to familiar approaches (De Falco et al., 2019). This suggests that PL neurons form part of the circuitry signaling approach to the correct, novel stimulus and the motor programs to receive reward (i.e., digging). Finally, we noted an error signal in a subset of putative pyramidal neurons when the rats made an error and dug in a familiar bowl. This change in firing was most prominent after digging was initiated, suggesting that it relates to monitoring of success on each trial of the OST. As performance of the OST is hippocampal independent (Dudchenko et al., 2000), these findings raise questions regarding how the firing patterns in dmPFC involved in action selection evolve in the absence of hippocampal interactions. One possibility is that hippocampal-dmPFC interactions are involved in the acquisition of the rule (i.e., search for the trial-unique novel odor) necessary for performance of the OST given the involvement of hippocampal networks in acquisition of some odor tasks (Martin et al., 2007).

In general, less is known about how the vmPFC is engaged in complex decision-making tasks. The focus on neural activity patterns in dmPFC may be due to the previously established role for that subregion in the adaptive actions (Euston et al., 2012). Altering synaptic plasticity in the glutamatergic projections from the IL cortex to NAc shell have been shown to affect decision making and valuation processes in the Restaurant Row task (Sweis et al., 2018), developed in Redish's laboratory (Steiner and Redish, 2014). In addition, the roles of connections between the dmPFC and vmPFC in more complex tasks have been examined in some studies. Most germane to the present discussion are the importance of interactions between the PL and IL for set-shifting (Mukherjee and Caroni, 2018). In this task, mice were required to dig in one of two bowls to receive a food reward. The bowls could be differentiated based on odors or the texture of the rims. Mice are trained on several discriminations that require switching between the cues and/or their modality (i.e., odor or texture). Results indicated a dissociation of function between these areas, with PL activity necessary for applying new rules and IL activity for shifting from rules that

were already acquired. Interestingly, projections from IL to PL appear critical for learning of alternative strategies in the task (Mukherjee and Caroni, 2018). Recent, related experiments examining the contribution of information in 4 subregions of the macaque mPFC support the assertion that information flows from the vmPFC to more dorsal areas in advance of a choice in a task that involves risky decision making for a reward (Maisson et al., 2021).

4.2. Novel approaches for understanding mPFC computational properties

To understand how dmPFC might encode various aspects of the decision making process, novel approaches are needed to identify the computational properties of this region. Various neuro-dynamical mechanisms have been proposed to underlie the decision-making process. One widespread model from the field of perceptual decision-making, describes decision-making as a leaky integration of evidence toward a decision threshold (Gold and Shadlen, 2007). At the neural level, it hypothesizes that choice-specific pools of neurons perform the integration through recurrent excitation, and once the firing rates of these accumulators reach a fixed threshold, this triggers a behavioral response such as a choice (Wang, 2008, 2012). Common to many decision-making models is that they are inherently dynamical systems models, and that the dynamics of decision circuits therefore can be effectively explored in a state space where the firing rates of neural ensembles are visualized together. Models of decision-making suggest that different choices in the state space are represented by different ‘attractors’, which are locations in state space that the neural trajectory flows towards (Albantakis and Deco, 2009; Deco et al., 2007; Wang, 2008). Upon reaching this region in the state space the trajectory will often dwell or swirl (Balaguer-Ballester et al., 2011; Lapish et al., 2015).

Computational models of delay discounting suggest that, when tested in two-alternative forced choice tasks, each option is encoded in a basin of attraction that firing patterns across a population of neurons will migrate towards during deliberation of the available options (Kurth-Nelson et al., 2012). Currently, these models account for several psychological variables that accompany the decision-making process, while contact with neural population dynamics is beginning to emerge. Attractors are hypothesized to be the result of strong connections between clusters of neurons (La Camera et al., 2019) as well as the byproduct of synaptic heterogeneity (Abeles et al., 1995; Seidemann et al., 1996; Rich and Wallis, 2016; La Camera et al., 2019). In addition, the activation of attractor-like activity (often referred to as metastable activity) allows an agent to anticipate forthcoming stimuli, which accelerates neural trajectories and decreases reaction times (Mazzucato et al., 2019). Therefore, the ability to implement these dynamical processes may be critical for the capacity to implement prospective strategies.

Methods to detect attractors and metastable neural activity states from in vivo data are rapidly improving (Durstewitz, 2017; Golub and Sussillo, 2018; Gilpin, 2020; Monfared and Durstewitz, 2020). Previous work identified attractor-like dynamics in the dmPFC of behaving rats, where neural trajectories moved between and dwelled in distinct regions of state space that were associated with the cognitive demands of the task (Lapish et al., 2015; Balaguer-Ballester et al., 2011). Further, the strength of attractor-like dynamics was systematically altered in a way that scaled with behavioral performance (Lapish et al., 2015;

Hashemnia et al., 2020). However, these studies relied on statistical dimensionality reduction approaches to reconstruct neural dynamics, which only allowed a descriptive account of the dynamics of the neural system.

Recently, more rigorous innovations in reconstructing neural systems using artificial intelligence and machine learning techniques have yielded promising results in capturing systems dynamics from in vivo neural recordings (Durstewitz, 2017; Pandarinath et al., 2018; Linderman et al., 2019; Sani et al., 2021), which now makes it possible to characterize neural dynamics in a more rigorous manner. These approaches typically recreate the dynamics of a neural system via a generative model (e.g., recurrent neural networks), which provides a closed form system. This allows for rigorous mathematical concepts developed in dynamic systems theory to be used to describe the system dynamics, which is more difficult when characterizing dynamics via statistical dimensionality reduction approaches (e.g., principal component analysis). The key next step in this process is to identify ways to use methods for reconstructing neural dynamics with increasing biological feasibility. Recurrent neural networks are constituted by simple nodes that possess a mere fraction of the biological intricacy of real neurons. Therefore, identifying ways to layer on biological feasibility may yield models capable of more expressive dynamics as one would expect in the brain. If successful, this could identify neural mechanisms that support complex forms of cognitive function such as strategy formation and decision-making.

5. Conclusions and future directions

In this review, we have discussed several different circuits that carry out computation in the mPFC (Fig. 1). In many ways, the mPFC serves as a confluence for inputs from different brain regions and links them to several different (mostly) limbic structures. It is, perhaps, this highly diffuse anatomical arrangement that allows the mPFC to influence such a wide array of behaviors and imbues it with wide-ranging patterns of neural activity. It is possible, even likely perhaps, that linking information across these circuits relies on computations that are implemented in population-level dynamics. The output structure of mPFC retains some level of unique selectivity in the efferent structure of each subregion. When considered with the fact that mPFC is highly recurrent, this suggests a role in linking several different behavioral processes. This combination of features creates unique challenges for understanding the function of this brain region, as heterogeneous inputs and outputs linked via recurrent drive, would be expected to generate a situation where several computations coexist close in time. Therefore, without a clear understanding of the underlying anatomical inputs and outputs of each unit, and the population-level computations they support, parsing these processes is an extremely difficult task. This requires the integration of circuit dissection techniques in combination with large scale neural recordings, so one can determine how computations are carried out across different subpopulations of neurons simultaneously.

It is our view that a greater understanding of the contributions of mPFC to adaptive behavior would be gained from future research priorities including:

1. A focus on conducting a granular analysis of the PL and IL with a view to identifying neuronal ensembles and their downstream targets that process and effect varied task demands. Applying advanced technologies in isolating discrete populations of mPFC cells with unique afferent and efferent connectivity and seeing how they contribute to adaptive behavior. Such experiments would be expected to reconcile the many discrepant findings in the conditioning literature.
2. Determine the role that recurrent connections in mPFC might play in linking and/or gating computational functions performed in anatomically distinct microcircuits. Manipulations of interneurons will likely be critical in achieving this goal. These subregions may also influence one another indirectly via spiraling PFC-dopaminergic pathways as between the striatum and VTA/SNc (Haber et al., 2000).
3. Much progress has been made in mapping the anatomical inputs and outputs of the mPFC. These efforts should continue with an eye towards function. Determining the functional connectivity patterns of mPFC microcircuits, and how they might evolve over time scales that behavior transpires, will be critical to identify motifs that support high-level cognitive functions.
4. Explorations of the role(s) of the mPFC-nucleus accumbens circuits in the acquisition and expression of avoidance behavior, natural reward-seeking, and decision-making during foraging, including in the OST are needed.
5. Better integration between the role of the mPFC in associative learning and higher cognitive demands and how they may inform each other.

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References

Abeles M, Bergman H, Gat I, Meilijson I, Seidemann E, Tishby N, Vaadia E, 1995. Corticalactivity flips among quasi-stationary states. Proc. Natl. Acad. Sci. USA 92 (19), 8616–8620. 10.1073/pnas.92.19.8616. [PubMed: 7567985]

Albantakis L, Deco G, 2009. The encoding of alternatives in multiple-choice decision making. Proc. Natl. Acad. Sci. USA 106, 10308–10313. [PubMed: 19497888]

Anastasiades PG, Carter AG, 2021. Circuit organization of the rodent medial prefrontal cortex. Trends Neurosci. 44, 550–563. [PubMed: 33972100]

Andersen RA, Cui H, 2009. Intention, action planning, and decision making in parietal-frontal circuits. Neuron 63, 568–583. [PubMed: 19755101]

Arruda-Carvalho M, Clem RL, 2014. Pathway-selective adjustment of prefrontal-amygdala transmission during fear encoding. J. Neurosci 34, 15601–15609. [PubMed: 25411488]

Arruda-Carvalho M, Clem RL, 2015. Prefrontal-amygdala fear networks come into focus. Front. Syst. Neurosci 9, 145. [PubMed: 26578902]

Ashwell R, Ito R, 2014. Excitotoxic lesions of the infralimbic, but not prelimbic cortex facilitate reversal of appetitive discriminative context conditioning: the role of the infralimbic cortex in context generalization. Front. Behav. Neurosci 8, 63. [PubMed: 24616678]

Augur IF, Wyckoff AR, Aston-Jones G, Kalivas PW, Peters J, 2016. Chemogenetic activation of an extinction neural circuit reduces cue-induced reinstatement of cocaine seeking. J. Neurosci 36, 10174–10180. [PubMed: 27683912]

Baeg EH, Kim YB, Jang J, Kim HT, Mook-Jung I, Jung MW, 2001. Fast spiking and regular spiking neural correlates of fear conditioning in the medial prefrontal cortex of the rat. Cereb. Cortex 11, 441–451. [PubMed: 11313296]

Balaguer-Ballester E, Lapish CC, Seamans JK, Durstewitz D, 2011. Attracting dynamics of frontal cortex ensembles during memory-guided decision-making. PLoS Comput. Biol 7, e1002057. [PubMed: 21625577]

Ball KT, Slane M, 2012. Differential involvement of prelimbic and infralimbic medial prefrontal cortex in discrete cue-induced reinstatement of 3,4-methylenedioxyme-thamphetamine (MDMA; ecstasy) seeking in rats. Psychopharmacology 224, 377–385. [PubMed: 22710489]

Balleine BW, Dickinson A, 1998. Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. Neuropharmacology 37, 407–419. [PubMed: 9704982]

Barker JM, Taylor JR, Chandler LJ, 2014. A unifying model of the role of the infralimbic cortex in extinction and habits. Learn. Mem 21, 441–448. [PubMed: 25128534]

Baxter MG, Murray EA, 2002. The amygdala and reward. Nat. Rev. Neurosci 3, 563–573. [PubMed: 12094212]

Berendse HW, Galis-de Graaf Y, Groenewegen HJ, 1992. Topographical organization and relationship with ventral striatal compartments of prefrontal corticostriatal projections in the rat. J. Comp. Neurol 316, 314–347. [PubMed: 1577988]

Berretta S, Pantazopoulos H, Caldera M, Pantazopoulos P, Pare D, 2005. Infralimbic cortex activation increases c-Fos expression in intercalated neurons of the amygdala. Neuroscience 132, 943–953. [PubMed: 15857700]

Bissonette GB, Roesch MR, 2017. Neurophysiology of rule switching in the corticostriatal circuit. Neuroscience 345, 64–76. [PubMed: 26851774]

Bloodgood DW, Sugam JA, Holmes A, Kash TL, 2018. Fear extinction requires infralimbic cortex projections to the basolateral amygdala. Transl. Psychiatry 8, 60. [PubMed: 29507292]

Bossert JM, Stern AL, Theberge FR, Cifani C, Koya E, et al. , 2011. Ventral medial prefrontal cortex neuronal ensembles mediate context-induced relapse to heroin. Nat. Neurosci 14, 420–422. [PubMed: 21336273]

Bossert JM, Stern AL, Theberge FR, Marchant NJ, Wang HL, et al. , 2012. Role of projections from ventral medial prefrontal cortex to nucleus accumbens shell in context-induced reinstatement of heroin seeking. J. Neurosci 32, 4982–4991. [PubMed: 22492053]

Boulay CB, Pieper F, Leavitt M, Martinez-Trujillo J, Sachs AJ, 2016. Single-trial decoding of intended eye movement goals from lateral prefrontal cortex neural ensembles. J. Neurophysiol 115, 486–499. [PubMed: 26561608]

Braver TS, 2012. The variable nature of cognitive control: a dual mechanisms framework. Trends Cogn. Sci 16, 106–113. [PubMed: 22245618]

Bravo-Rivera C, Roman-Ortiz C, Brignoni-Perez E, Sotres-Bayon F, Quirk GJ, 2014. Neural structures mediating expression and extinction of platform-mediated avoidance. J. Neurosci 34, 9736–9742. [PubMed: 25031411]

Brockett AT, Roesch MR, 2021. Reactive and proactive adaptation of cognitive and motor neural signals during performance of a stop-change task. Brain Sci. 11.

Brockett AT, Hricz NW, Tennyson SS, Bryden DW, Roesch MR, 2020. Neural signals in red nucleus during reactive and proactive adjustments in behavior. J. Neurosci 40, 4715–4726. [PubMed: 32376779]

Bukalo O, Pinard CR, Silverstein S, Brehm C, Hartley ND, et al. , 2015. Prefrontal inputs to the amygdala instruct fear extinction memory formation. Sci. Adv 1.

Burgos-Robles A, Vidal-Gonzalez I, Quirk GJ, 2009. Sustained conditioned responses in prelimbic prefrontal neurons are correlated with fear expression and extinction failure. J. Neurosci 29, 8474–8482. [PubMed: 19571138]

Caballero JP, Scarpa GB, Remage-Healey L, Moorman DE, 2019. Differential effects of dorsal and ventral medial prefrontal cortex inactivation during natural reward seeking, extinction, and cue-induced reinstatement. eNeuro 6.

Calu DJ, Kawa AB, Marchant NJ, Navarre BM, Henderson MJ, et al. , 2013. Optogenetic inhibition of dorsal medial prefrontal cortex attenuates stress-induced reinstatement of palatable food seeking in female rats. J. Neurosci 33, 214–226. [PubMed: 23283335]

Cameron CM, Murugan M, Choi JY, Engel EA, Witten IB, 2019. Increased cocaine motivation is associated with degraded spatial and temporal representations in IL-NAc neurons. Neuron 103, 80–91 e7. [PubMed: 31101395]

Capriles N, Rodaros D, Sorge RE, Stewart J, 2003. A role for the prefrontal cortex in stress- and cocaine-induced reinstatement of cocaine seeking in rats. Psychopharmacology 168, 66–74. [PubMed: 12442201]

Capuzzo G, Floresco SB, 2020. Prelimbic and infralimbic prefrontal regulation of active and inhibitory avoidance and reward-seeking. J. Neurosci 40, 4773–4787. [PubMed: 32393535]

Carr DB, Sesack SR, 2000. Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. J. Neurosci 20, 3864–3873. [PubMed: 10804226]

Catanese J, Viggiano A, Cerasti E, Zugaro MB, Wiener SI, 2014. Retrospectively and prospectively modulated hippocampal place responses are differentially distributed along a common path in a continuous T-maze. J. Neurosci 34, 13163–13169. [PubMed: 25253861]

Chang JY, Sawyer SF, Paris JM, Kirillov A, Woodward DJ, 1997. Single neuronal responses in medial prefrontal cortex during cocaine self-administration in freely moving rats. Synapse 26, 22–35. [PubMed: 9097402]

Chen W, Wang Y, Sun A, Zhou L, Xu W, et al. , 2016. Activation of AMPA receptor in the infralimbic cortex facilitates extinction and attenuates the heroin-seeking behavior in rats. Neurosci. Lett 612, 126–131. [PubMed: 26639425]

Chen X, Scangos KW, Stuphorn V, 2010. Supplementary motor area exerts proactive and reactive control of arm movements. J. Neurosci 30, 14657–14675. [PubMed: 21048123]

Cho JH, Deisseroth K, Bolshakov VY, 2013. Synaptic encoding of fear extinction in mPFC-amygdala circuits. Neuron 80, 1491–1507. [PubMed: 24290204]

Churchland MM, Cunningham JP, Kaufman MT, Foster JD, Nuyujukian P, et al. , 2012. Neural population dynamics during reaching. Nature 487, 51–56. [PubMed: 22722855]

Churchwell JC, Kesner RP, 2011. Hippocampal-prefrontal dynamics in spatial working memory: interactions and independent parallel processing. Behav. Brain Res 225, 389–395. [PubMed: 21839780]

Cook RG, Brown MF, Riley DA, 1985. Flexible memory processing by rats: use of prospective and retrospective information in the radial maze. J. Exp. Psychol. Anim. Behav. Process 11, 453–469. [PubMed: 4009126]

Corbit LH, Nie H, Janak PH, 2012. Habitual alcohol seeking: time course and the contribution of subregions of the dorsal striatum. Biol. Psychiatry 72, 389–395. [PubMed: 22440617]

Cui Y, Jin J, Zhang X, Xu H, Yang L, et al. , 2011. Forebrain NR2B overexpression facilitating the prefrontal cortex long-term potentiation and enhancing working memory function in mice. PLoS One 6, e20312. [PubMed: 21655294]

Cunningham JP, Yu BM, 2014. Dimensionality reduction for large-scale neural recordings. Nat. Neurosci 17, 1500–1509. [PubMed: 25151264]

Dalley JW, Everitt BJ, Robbins TW, 2011. Impulsivity, compulsivity, and top-down cognitive control. Neuron 69, 680–694. [PubMed: 21338879]

Davies DA, Greba Q, Howland JG, 2013a. GluN2B-containing NMDA receptors and AMPA receptors in medial prefrontal cortex are necessary for odor span in rats. Front. Behav. Neurosci 7, 183. [PubMed: 24348356]

Davies DA, Molder JJ, Greba Q, Howland JG, 2013b. Inactivation of medial prefrontal cortex or acute stress impairs odor span in rats. Learn. Mem 20, 665–669. [PubMed: 24241748]

Davies DA, Greba Q, Selk JC, Catton JK, Baillie LD, et al. , 2017. Interactions between medial prefrontal cortex and dorsomedial striatum are necessary for odor span capacity in rats: role of GluN2B-containing NMDA receptors. Learn. Mem 24, 524–531. [PubMed: 28916627]

De Falco E, An L, Sun N, Roebuck AJ, Greba Q, et al. , 2019. The rat medial prefrontal cortex exhibits flexible neural activity states during the performance of an odor span task. eNeuro 6.

Deco G, Scarano L, Soto-Faraco S, 2007. Weber's law in decision making: integrating behavioral data in humans with a neurophysiological model. J. Neurosci 27, 11192–11200. [PubMed: 17942714]

Di Pietro NC, Black YD, Kantak KM, 2006. Context-dependent prefrontal cortex regulation of cocaine self-administration and reinstatement behaviors in rats. Eur. J. Neurosci 24, 3285–3298. [PubMed: 17156389]

Diehl MM, Bravo-Rivera C, Rodriguez-Romaguera J, Pagan-Rivera PA, Burgos-Robles A, et al. , 2018. Active avoidance requires inhibitory signaling in the rodent prelimbic prefrontal cortex. elife 7.

Do-Monte FH, Manzano-Nieves G, Quinones-Laracuente K, Ramos-Medina L, Quirk GJ, 2015a. Revisiting the role of infralimbic cortex in fear extinction with optogenetics. J. Neurosci 35, 3607–3615. [PubMed: 25716859]

Do-Monte FH, Quinones-Laracuente K, Quirk GJ, 2015b. A temporal shift in the circuits mediating retrieval of fear memory. Nature 519, 460–463. [PubMed: 25600268]

Dudchenko PA, 2004. An overview of the tasks used to test working memory in rodents. Neurosci. Biobehav. Rev 28, 699–709. [PubMed: 15555679]

Dudchenko PA, Wood ER, Eichenbaum H, 2000. Neurotoxic hippocampal lesions have no effect on odor span and little effect on odor recognition memory but produce significant impairments on spatial span, recognition, and alternation. J. Neurosci 20, 2964–2977. [PubMed: 10751449]

Dudchenko PA, Talpos J, Young J, Baxter MG, 2013. Animal models of working memory: a review of tasks that might be used in screening drug treatments for the memory impairments found in schizophrenia. Neurosci. Biobehav. Rev 37, 2111–2124. [PubMed: 22464948]

Durstewitz D, 2017. Astate space approach for piecewise-linear recurrent neural networks foridentifying computational dynamics from neural measurements. PLoS Comput. Biol 13 (6), e1005542 10.1371/journal.pcbi.1005542 eCollection 2017 Jun. [PubMed: 28574992]

Durstewitz D, Vittoz NM, Floresco SB, Seamans JK, 2010. Abrupt transitions between prefrontal neural ensemble states accompany behavioral transitions during rule learning. Neuron 66, 438–448. [PubMed: 20471356]

Eddy MC, Todd TP, Bouton ME, Green JT, 2016. Medial prefrontal cortex involvement in the expression of extinction and ABA renewal of instrumental behavior for a food reinforcer. Neurobiol. Learn. Mem 128, 33–39. [PubMed: 26723281]

Euston DR, Gruber AJ, McNaughton BL, 2012. The role of medial prefrontal cortex in memory and decision making. Neuron 76, 1057–1070. [PubMed: 23259943]

Ferbinteanu J, Shapiro ML, 2003. Prospective and retrospective memory coding in the hippocampus. Neuron 40, 1227–1239. [PubMed: 14687555]

Fitzgerald PJ, Whittle N, Flynn SM, Graybeal C, Pinard CR, et al. , 2014. Prefrontal single-unit firing associated with deficient extinction in mice. Neurobiol. Learn. Mem 113, 69–81. [PubMed: 24231425]

Floresco SB, 2015. The nucleus accumbens: an interface between cognition, emotion, and action. Annu. Rev. Psychol 66, 25–52. [PubMed: 25251489]

Floresco SB, Seamans JK, Phillips AG, 1997. Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. J. Neurosci 17, 1880–1890. [PubMed: 9030646]

Fuchs RA, Evans KA, Ledford CC, Parker MP, Case JM, et al. , 2005. The role of the dorsomedial prefrontal cortex, basolateral amygdala, and dorsal hippocampus in contextual reinstatement of cocaine seeking in rats. Neuropsychopharmacology 30, 296–309. [PubMed: 15483559]

Gabbott PL, Warner TA, Jays PR, Salway P, Busby SJ, 2005. Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. J. Comp. Neurol 492, 145–177. [PubMed: 16196030]

Gass JT, Trantham-Davidson H, Kassab AS, Glen WB Jr., Olive MF, Chandler LJ, 2014. Enhancement of extinction learning attenuates ethanol-seeking behavior and alters plasticity in the prefrontal cortex. J. Neurosci 34, 7562–7574. [PubMed: 24872560]

Gentry RN, Roesch MR, 2018. Neural activity in ventral medial prefrontal cortex is modulated more before approach than avoidance during reinforced and extinction trial blocks. J. Neurosci 38, 4584–4597. [PubMed: 29661965]

Ghazizadeh A, Ambroggi F, Odean N, Fields HL, 2012. Prefrontal cortex mediates extinction of responding by two distinct neural mechanisms in accumbens shell. J. Neurosci 32, 726–737. [PubMed: 22238108]

Gilmartin MR, McEchron MD, 2005. Single neurons in the medial prefrontal cortex of the rat exhibit tonic and phasic coding during trace fear conditioning. Behav. Neurosci 119, 1496–1510. [PubMed: 16420154]

Gilpin W, 2020. Deep reconstructionof strange attractors from time series. In: Larochelle H, Ranzato M, Hadsell R, Balcan MF, Lin H (Eds.), Advances in Neural Information Processing Systems, 33. NeurIPS 2020.

Gisquet-Verrier P, Delatour B, 2006. The role of the rat prelimbic/infralimbic cortex in working memory: not involved in the short-term maintenance but in monitoring and processing functions. Neuroscience 141, 585–596. [PubMed: 16713111]

Giustino TF, Fitzgerald PJ, Maren S, 2016. Fear expression suppresses medial prefrontal cortical firing in rats. PLoS One 11, e0165256. [PubMed: 27776157]

Gold JI, Shadlen MN, 2007. The neural basis of decision making. Annu. Rev. Neurosci 30, 535–574. [PubMed: 17600525]

Golub MD, Sussillo D, 2018. Fixed Point Finder: A Tensorflow toolbox for identifying and characterizing fixed points in recurrent neural networks. J. Open Source Softw 3 (31), 1003.

Goto Y, Grace AA, 2008. Dopamine modulation of hippocampal-prefrontal cortical interaction drives memory-guided behavior. Cereb. Cortex 18, 1407–1414. [PubMed: 17934187]

Gourley SL, Taylor JR, 2016. Going and stopping: dichotomies in behavioral control by the prefrontal cortex. Nat. Neurosci 19, 656–664. [PubMed: 29162973]

Gutman AL, Ewald VA, Cosme CV, Worth WR, LaLumiere RT, 2017a. The infralimbic and prelimbic cortices contribute to the inhibitory control of cocaine-seeking behavior during a discriminative stimulus task in rats. Addict. Biol 22, 1719–1730. [PubMed: 27549035]

Gutman AL, Nett KE, Cosme CV, Worth WR, Gupta SC, et al. , 2017b. Extinction of cocaine seeking requires a window of infralimbic pyramidal neuron activity after unreinforced lever presses. J. Neurosci 37, 6075–6086. [PubMed: 28539416]

Haber SN, Fudge JL, McFarland NR, 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J. Neurosci 20, 2369–2382. [PubMed: 10704511]

Haddon JE, Killcross AS, 2005. Medial prefrontal cortex lesions abolish contextual control of competing responses. J. Exp. Anal. Behav 84, 485–504. [PubMed: 16596976]

Hashemnia S, Euston DR, Gruber AJ, 2020. Amphetamine reduces reward encoding and stabilizes neural dynamics in rat anterior cingulate cortex. Elife 19 (9), e56755. 10.7554/eLife.56755.

Hayen A, Meese-Tamuri S, Gates A, Ito R, 2014. Opposing roles of prelimbic and infralimbic dopamine in conditioned cue and place preference. Psychopharmacology 231, 2483–2492. [PubMed: 24429871]

Hoover WB, Vertes RP, 2007. Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. Brain Struct. Funct 212, 149–179. [PubMed: 17717690]

Hunnicutt BJ, Jongbloets BC, Birdsong WT, Gertz KJ, Zhong H, Mao T, 2016. A comprehensive excitatory input map of the striatum reveals novel functional organization. elife 5.

Isaac WL, Nonneman AJ, Neisewander J, Landers T, Bardo MT, 1989. Prefrontal cortex lesions differentially disrupt cocaine-reinforced conditioned place preference but not conditioned taste aversion. Behav. Neurosci 103, 345–355. [PubMed: 2706078]

Ishikawa A, Ambroggi F, Nicola SM, Fields HL, 2008a. Contributions of the amygdala and medial prefrontal cortex to incentive cue responding. Neuroscience 155, 573–584. [PubMed: 18640246]

Ishikawa A, Ambroggi F, Nicola SM, Fields HL, 2008b. Dorsomedial prefrontal cortex contribution to behavioral and nucleus accumbens neuronal responses to incentive cues. J. Neurosci 28, 5088–5098. [PubMed: 18463262]

Ito HT, Zhang SJ, Witter MP, Moser EI, Moser MB, 2015. A prefrontal-thalamo-hippocampal circuit for goal-directed spatial navigation. Nature 522, 50–55. [PubMed: 26017312]

Itskov V, Pastalkova E, Mizuseki K, Buzsaki G, Harris KD, 2008. Theta-mediated dynamics of spatial information in hippocampus. J. Neurosci 28, 5959–5964. [PubMed: 18524900]

James MH, McGlinchey EM, Vattikonda A, Mahler SV, Aston-Jones G, 2018. Cued reinstatement of cocaine but not sucrose seeking is dependent on dopamine signaling in prelimbic cortex and is associated with recruitment of prelimbic neurons that project to contralateral nucleus accumbens core. Int. J. Neuropsychopharmacol 21, 89–94. [PubMed: 29165565]

Jiang ZC, Pan Q, Zheng C, Deng XF, Wang JY, Luo F, 2014. Inactivation of the prelimbic rather than infralimbic cortex impairs acquisition and expression of formalin-induced conditioned place avoidance. Neurosci. Lett 569, 89–93. [PubMed: 24726402]

Jones BF, Groenewegen HJ, Witter MP, 2005. Intrinsic connections of the cingulate cortex in the rat suggest the existence of multiple functionally segregated networks. Neuroscience 133, 193–207. [PubMed: 15893643]

Keistler C, Barker JM, Taylor JR, 2015. Infralimbic prefrontal cortex interacts with nucleus accumbens shell to unmask expression of outcome-selective Pavlovian-to-instrumental transfer. Learn. Mem 22, 509–513. [PubMed: 26373829]

Kesner RP, 1989. Retrospective and prospective coding of information: role of the medial prefrontal cortex. Exp. Brain Res 74, 163–167. [PubMed: 2924832]

Khoo SY, Sciascia JM, Pettorelli A, Maddux JN, Chaudhri N, 2019. The medial prefrontal cortex is required for responding to alcohol-predictive cues but only in the absence of alcohol delivery. J. Psychopharmacol 33, 842–854. [PubMed: 31070082]

Kim SC, Jo YS, Kim IH, Kim H, Choi JS, 2010. Lack of medial prefrontal cortex activation underlies the immediate extinction deficit. J. Neurosci 30, 832–837. [PubMed: 20089891]

Knapska E, Maren S, 2009. Reciprocal patterns of c-Fos expression in the medial prefrontal cortex and amygdala after extinction and renewal of conditioned fear. Learn. Mem 16, 486–493. [PubMed: 19633138]

Kurikawa T, Haga T, Handa T, Harukuni R, Fukai T, 2018. Neuronal stability in medial frontal cortex sets individual variability in decision-making. Nat. Neurosci 21, 1764–1773. [PubMed: 30420732]

Kurth-Nelson Z, Bickel W, Redish AD, 2012. A theoretical account of cognitive effects in delay discounting. Eur. J. Neurosci 35, 1052–1064. [PubMed: 22487035]

La Camera G, Fontanini A, Mazzucato L, 2019. Cortical computations via metastable activity. Curr. Opin. Neurobiol 58, 37–45. 10.1016/j.conb.2019.06.007. Epub 2019 Jul 18. [PubMed: 31326722]

LaLumiere RT, Kalivas PW, 2008. Glutamate release in the nucleus accumbens core is necessary for heroin seeking. J. Neurosci 28, 3170–3177. [PubMed: 18354020]

LaLumiere RT, Smith KC, Kalivas PW, 2012. Neural circuit competition in cocaine-seeking: roles of the infralimbic cortex and nucleus accumbens shell. Eur. J. Neurosci 35, 614–622. [PubMed: 22321070]

Lapish CC, Balaguer-Ballester E, Seamans JK, Phillips AG, Durstewitz D, 2015. Amphetamine exerts dose-dependent changes in prefrontal cortex attractor dynamics during working memory. J. Neurosci 35, 10172–10187. [PubMed: 26180194]

Laque A, Ness GLD, Wagner GE, Nedelescu H, Carroll A, et al. , 2019. Anti-relapse neurons in the infralimbic cortex of rats drive relapse-suppression by drug omission cues. Nat. Commun 10, 3934. [PubMed: 31477694]

Laubach M, Amarante LM, Swanson K, White SR, 2018. What, if anything, is rodent prefrontal cortex? eNeuro 5.

Laurent V, Westbrook RF, 2009. Inactivation of the infralimbic but not the prelimbic cortex impairs consolidation and retrieval of fear extinction. Learn. Mem 16, 520–529. [PubMed: 19706835]

Laurent V, Chieng B, Balleine BW, 2016. Extinction generates outcome-specific conditioned inhibition. Curr. Biol 26, 3169–3175. [PubMed: 28094035]

Lay BP, Pitaru AA, Boulianne N, Esber GR, Iordanova MD, 2020. Different methods of fear reduction are supported by distinct cortical substrates. elife 9.

Lay BPP, Nicolosi M, Usypchuk AA, Esber GR, Iordanova MD, 2019. Dissociation of appetitive overexpectation and extinction in the infralimbic cortex. Cereb. Cortex 29, 3687–3701. [PubMed: 30371757]

Lebron K, Milad MR, Quirk GJ, 2004. Delayed recall of fear extinction in rats with lesions of ventral medial prefrontal cortex. Learn. Mem 11, 544–548. [PubMed: 15466306]

Levesque M, Parent A, 1998. Axonal arborization of corticostriatal and corticothalamic fibers arising from prelimbic cortex in the rat. Cereb. Cortex 8, 602–613. [PubMed: 9823481]

Levy DA, Manns JR, Hopkins RO, Gold JJ, Broadbent NJ, Squire LR, 2003. Impaired visual and odor recognition memory span in patients with hippocampal lesions. Learn. Mem 10, 531–536. [PubMed: 14657265]

Linderman SW, Nichols ALA, Blei DM, Zimmer M and Paninski L (2019). Hierarchical recurrent state spacemodels reveal discrete and continuous dynamics of neural activity in C.elegans. BioRxiv. 10.1101/621540.

Lingawi NW, Westbrook RF, Laurent V, 2017. Extinction and latent inhibition involve a similar form of inhibitory learning that is stored in and retrieved from the infralimbic cortex. Cereb. Cortex 27, 5547–5556. [PubMed: 27797830]

Lingawi NW, Holmes NM, Westbrook RF, Laurent V, 2018. The infralimbic cortex encodes inhibition irrespective of motivational significance. Neurobiol. Learn. Mem 150, 64–74. [PubMed: 29518495]

Linsenbardt DN, Timme NM, Lapish CC, 2019. Encoding of the intent to drink alcohol by the prefrontal cortex is blunted in rats with a family history of excessive drinking. eNeuro 6.

Linsenbardt DN, Smoker MP, Janetsian-Fritz SS, Lapish CC, 2017. Impulsivity in rodents with a genetic predisposition for excessive alcohol consumption is associated with a lack of a prospective strategy. Cogn. Affect. Behav. Neurosci 17, 235–251. [PubMed: 28000083]

Ma YY, Lee BR, Wang X, Guo C, Liu L, et al. , 2014. Bidirectional modulation of incubation of cocaine craving by silent synapse-based remodeling of prefrontal cortex to accumbens projections. Neuron 83, 1453–1467. [PubMed: 25199705]

Maisson DJ, Cash-Padgett TV, Wang MZ, Hayden BY, Heilbronner SR, Zimmermann J, 2021. Choice-relevant information transformation along a ventrodorsal axis in the medial prefrontal cortex. Nat. Commun 12, 4830. [PubMed: 34376663]

Mante V, Sussillo D, Shenoy KV, Newsome WT, 2013. Context-dependent computation by recurrent dynamics in prefrontal cortex. Nature 503, 78–84. [PubMed: 24201281]

Marek R, Xu L, Sullivan RKP, Sah P, 2018. Excitatory connections between the prelimbic and infralimbic medial prefrontal cortex show a role for the prelimbic cortex in fear extinction. Nat. Neurosci 21, 654–658. [PubMed: 29686260]

Marquis JP, Killcross S, Haddon JE, 2007. Inactivation of the prelimbic, but not infralimbic, prefrontal cortex impairs the contextual control of response conflict in rats. Eur. J. Neurosci 25, 559–566. [PubMed: 17284198]

Martin C, Beshel J, Kay LM, 2007. An olfacto-hippocampal network is dynamically involved in odor-discrimination learning. J. Neurophysiol 98, 2196–2205. [PubMed: 17699692]

Mazzucato L, La Camera G, Fontanini A, 2019. Expectation-inducedmodulation of metastable activity underlies faster coding of sensory stimuli. Nat. Neurosci 22 (5), 787–796. 10.1038/s41593-019-0364-9. Epub 2019 Apr 1. [PubMed: 30936557]

McFarland K, Kalivas PW, 2001. The circuitry mediating cocaine-induced reinstatement of drug-seeking behavior. J. Neurosci 21, 8655–8663. [PubMed: 11606653]

McFarland K, Lapish CC, Kalivas PW, 2003. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. J. Neurosci 23, 3531–3537. [PubMed: 12716962]

McFarland K, Davidge SB, Lapish CC, Kalivas PW, 2004. Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. J. Neurosci 24, 1551–1560. [PubMed: 14973230]

McGlinchey EM, James MH, Mahler SV, Pantazis C, Aston-Jones G, 2016. Prelimbic to accumbens core pathway is recruited in a dopamine-dependent manner to drive cued reinstatement of cocaine seeking. J. Neurosci 36, 8700–8711. [PubMed: 27535915]

McLaughlin J, See RE, 2003. Selective inactivation of the dorsomedial prefrontal cortex and the basolateral amygdala attenuates conditioned-cued reinstatement of extinguished cocaine-seeking behavior in rats. Psychopharmacology 168, 57–65. [PubMed: 12845418]

Mendoza J, Sanio C, Chaudhri N, 2015. Inactivating the infralimbic but not prelimbic medial prefrontal cortex facilitates the extinction of appetitive Pavlovian conditioning in Long-Evans rats. Neurobiol. Learn. Mem 118, 198–208. [PubMed: 25543024]

Milad MR, Quirk GJ, 2002. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature 420, 70–74. [PubMed: 12422216]

Milad MR, Vidal-Gonzalez I, Quirk GJ, 2004. Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. Behav. Neurosci 118, 389–394. [PubMed: 15113265]

Miller CA, Marshall JF, 2004. Altered prelimbic cortex output during cue-elicited drug seeking. J. Neurosci 24, 6889–6897. [PubMed: 15295023]

Momennejad I, Haynes JD, 2013. Encoding of prospective tasks in the human prefrontal cortex under varying task loads. J. Neurosci 33, 17342–17349. [PubMed: 24174667]

Monfared Z and Durstewitz D (2020). Transformation of ReLU-based recurrent neural networks from discrete-time to continuous-time. Proceedings of the 37th International Conference on Machine Learning, in Proceedings of Machine Learning Research 119: 6999–7009 Available from https://proceedings.mlr.press/v119/monfared20a.html.

Moorman DE, Aston-Jones G, 2015. Prefrontal neurons encode context-based response execution and inhibition in reward seeking and extinction. Proc. Natl. Acad. Sci. USA 112, 9472–9477. [PubMed: 26170333]

Morgan MA, Schulkin J, LeDoux JE, 2003. Ventral medial prefrontal cortex and emotional perseveration: the memory for prior extinction training. Behav. Brain. Res 146, 121–130. [PubMed: 14643465]

Moscarello JM, LeDoux JE, 2013. Active avoidance learning requires prefrontal suppression of amygdala-mediated defensive reactions. J. Neurosci 33, 3815–3823. [PubMed: 23447593]

Mukherjee A, Caroni P, 2018. Infralimbic cortex is required for learning alternatives to prelimbic promoted associations through reciprocal connectivity. Nat. Commun 9, 2727. [PubMed: 30006525]

Murray BG, Davies DA, Molder JJ, Howland JG, 2017. Maternal immune activation during pregnancy in rats impairs working memory capacity of the offspring. Neurobiol. Learn. Mem 141, 150–156. [PubMed: 28434949]

Myroshnychenko M, Seamans JK, Phillips AG, Lapish CC, 2017. Temporal dynamics of hippocampal and medial prefrontal cortex interactions during the delay period of a working memory-guided foraging task. Cereb. Cortex 27, 5331–5342. [PubMed: 28927240]

O'Hare JK, Ade KK, Sukharnikova T, Van Hooser SD, Palmeri ML, et al. , 2016. Pathway-specific striatal substrates for habitual behavior. Neuron 89, 472–479. [PubMed: 26804995]

Otis JM, Namboodiri VM, Matan AM, Voets ES, Mohorn EP, et al. , 2017. Prefrontal cortex output circuits guide reward seeking through divergent cue encoding. Nature 543, 103–107. [PubMed: 28225752]

Ovari J, Leri F, 2008. Inactivation of the ventromedial prefrontal cortex mimics re-emergence of heroin seeking caused by heroin reconditioning. Neurosci. Lett 444, 52–55. [PubMed: 18706971]

Pandarinath C, O'Shea DJ, Collins J, Jozefowicz R, Stavisky SD, Kao JC, Trautmann EM, Kaufman MT, Ryu SI, Hochberg LR, Henderson JM, Shenoy KV, Abbott LF, Sussillo D, 2018. Inferringsingle-trial neural population dynamics using sequential auto-encoders. Nat. Methods 15 (10), 805–815. 10.1038/s41592-018-0109-9. Epub 2018 Sep 17. [PubMed: 30224673]

Pascoli V, Terrier J, Espallergues J, Valjent E, O'Connor EC, Luscher C, 2014. Contrasting forms of cocaine-evoked plasticity control components of relapse. Nature 509, 459–464. [PubMed: 24848058]

Peak J, Chieng B, Hart G, Balleine BW, 2020. Striatal direct and indirect pathway neurons differentially control the encoding and updating of goal-directed learning. elife 9.

Peters AJ, Fabre JMJ, Steinmetz NA, Harris KD, Carandini M, 2021. Striatal activity topographically reflects cortical activity. Nature 591, 420–425. [PubMed: 33473213]

Peters J, LaLumiere RT, Kalivas PW, 2008. Infralimbic prefrontal cortex is responsible for inhibiting cocaine seeking in extinguished rats. J. Neurosci 28, 6046–6053. [PubMed: 18524910]

Peters J, Kalivas PW, Quirk GJ, 2009. Extinction circuits for fear and addiction overlap in prefrontal cortex. Learn. Mem 16, 279–288. [PubMed: 19380710]

Peters J, Dieppa-Perea LM, Melendez LM, Quirk GJ, 2010. Induction of fear extinction with hippocampal-infralimbic BDNF. Science 328, 1288–1290. [PubMed: 20522777]

Pfarr S, Meinhardt MW, Klee ML, Hansson AC, Vengeliene V, et al. , 2015. Losing control: excessive alcohol seeking after selective inactivation of cue-responsive neurons in the infralimbic cortex. J. Neurosci 35, 10750–10761. [PubMed: 26224858]

Pfarr S, Schaaf L, Reinert JK, Paul E, Herrmannsdorfer F, et al. , 2018. Choice for drug or natural reward engages largely overlapping neuronal ensembles in the infralimbic prefrontal Cortex. J. Neurosci 38, 3507–3519. [PubMed: 29483279]

Pfeiffer BE, Foster DJ, 2013. Hippocampal place-cell sequences depict future paths to remembered goals. Nature 497, 74–79. [PubMed: 23594744]

Pratt WE, Mizumori SJ, 2001. Neurons in rat medial prefrontal cortex show anticipatory rate changes to predictable differential rewards in a spatial memory task. Behav. Brain Res 123, 165–183. [PubMed: 11399329]

Quirk GJ, Mueller D, 2008. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology 33, 56–72. [PubMed: 17882236]

Quirk GJ, Russo GK, Barron JL, Lebron K, 2000. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. J. Neurosci 20, 6225–6231. [PubMed: 10934272]

Quirk GJ, Likhtik E, Pelletier JG, Pare D, 2003. Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. J. Neurosci 23, 8800–8807. [PubMed: 14507980]

Redish AD, 2016. Vicarious trial and error. Nat. Rev. Neurosci 17, 147–159. [PubMed: 26891625]

Rhodes SE, Killcross S, 2004. Lesions of rat infralimbic cortex enhance recovery and reinstatement of an appetitive Pavlovian response. Learn. Mem 11, 611–616. [PubMed: 15466316]

Rhodes SE, Killcross AS, 2007a. Lesions of rat infralimbic cortex enhance renewal of extinguished appetitive Pavlovian responding. Eur. J. Neurosci 25, 2498–2503. [PubMed: 17445245]

Rhodes SE, Killcross AS, 2007b. Lesions of rat infralimbic cortex result in disrupted retardation but normal summation test performance following training on a Pavlovian conditioned inhibition procedure. Eur. J. Neurosci 26, 2654–2660. [PubMed: 17970744]

Riaz S, Puveendrakumaran P, Khan D, Yoon S, Hamel L, Ito R, 2019. Prelimbic and infralimbic cortical inactivations attenuate contextually driven discriminative responding for reward. Sci. Rep 9, 3982. [PubMed: 30850668]

Rich EL, Wallis JD, 2016. Decoding subjective decisions from orbitofrontal cortex. Nat. Neurosci 19 (7), 973–980. 10.1038/nn.4320. Epub 2016 Jun 6. [PubMed: 27273768]

Rogers JL, Ghee S, See RE, 2008. The neural circuitry underlying reinstatement of heroin-seeking behavior in an animal model of relapse. Neuroscience 151, 579–588. [PubMed: 18061358]

Rubio FJ, Quintana-Feliciano R, Warren BL, Li X, Witonsky KFR, et al. , 2019. Prelimbic cortex is a common brain area activated during cue-induced reinstatement of cocaine and heroin seeking in a polydrug self-administration rat model. Eur. J. Neurosci 49, 165–178. [PubMed: 30307667]

Sakagami M, Niki H, 1994. Encoding of behavioral significance of visual stimuli by primate prefrontal neurons: relation to relevant task conditions. Exp. Brain Res 97, 423–436. [PubMed: 8187854]

Sakagami M, Tsutsui K, 1999. The hierarchical organization of decision making in the primate prefrontal cortex. Neurosci. Res 34, 79–89. [PubMed: 10498334]

Sangha S, Robinson PD, Greba Q, Davies DA, Howland JG, 2014. Alterations in reward, fear and safety cue discrimination after inactivation of the rat prelimbic and infralimbic cortices. Neuropsychopharmacology 39, 2405–2413. [PubMed: 24727732]

Sani OG, Abbaspourazad H, Wong YT, Pesaran B, Shanechi MM, 2021. Modeling behaviorally relevant neural dynamics enabled by preferential subspace identification. Nat. Neurosci 24 (1), 140–149. 10.1038/s41593-020-00733-0. [PubMed: 33169030]

Schmidt B, Duin AA, Redish AD, 2019. Disrupting the medial prefrontal cortex alters hippocampal sequences during deliberative decision making. J. Neurophysiol 121, 1981–2000. [PubMed: 30892976]

Scott GA, Zabder NK, Greba Q, Howland JG, 2018. Performance of the odour span task is not impaired following inactivations of parietal cortex in rats. Behav. Brain Res 341, 181–188. [PubMed: 29247751]

Scott GA, Liu MC, Tahir NB, Zabder NK, Song Y, et al. , 2020. Roles of the medial prefrontal cortex, mediodorsal thalamus, and their combined circuit for performance of the odor span task in rats: analysis of memory capacity and foraging behavior. Learn. Mem 27, 67–77. [PubMed: 31949038]

Sierra-Mercado D, Padilla-Coreano N, Quirk GJ, 2011. Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. Neuropsychopharmacology 36, 529–538. [PubMed: 20962768]

Sierra-Mercado D Jr., Corcoran KA, Lebron-Milad K, Quirk GJ, 2006. Inactivation of the ventromedial prefrontal cortex reduces expression of conditioned fear and impairs subsequent recall of extinction. Eur. J. Neurosci 24, 1751–1758. [PubMed: 17004939]

Seidemann E, Meilijson I, Abeles M, Bergman H, Vaadia E, 1996. Simultaneouslyrecorded single units in the frontal cortex go through sequences of discreteand stable states in monkeys performing a delayed localization task. J. Neurosci 16 (2), 752–768. 10.1523/JNEUROSCI.16-02-00752.1996. [PubMed: 8551358]

Stefanik MT, Kupchik YM, Kalivas PW, 2016. Optogenetic inhibition of cortical afferents in the nucleus accumbens simultaneously prevents cue-induced transient synaptic potentiation and cocaine-seeking behavior. Brain Struct. Funct 221, 1681–1689. [PubMed: 25663648]

Stefanik MT, Moussawi K, Kupchik YM, Smith KC, Miller RL, et al. , 2013. Optogenetic inhibition of cocaine seeking in rats. Addict. Biol 18, 50–53. [PubMed: 22823160]

Steiner AP, Redish AD, 2014. Behavioral and neurophysiological correlates of regret in rat decision-making on a neuroeconomic task. Nat. Neurosci 17, 995–1002. [PubMed: 24908102]

Strobel C, Marek R, Gooch HM, Sullivan RKP, Sah P, 2015. Prefrontal and auditory input to intercalated neurons of the amygdala. Cell Rep. 10, 1435–1442. [PubMed: 25753409]

Sussillo D, 2014. Neural circuits as computational dynamical systems. Curr. Opin. Neurobiol 25, 156–163. [PubMed: 24509098]

Suto N, Laque A, De Ness GL, Wagner GE, Watry D, et al. , 2016. Distinct memory engrams in the infralimbic cortex of rats control opposing environmental actions on a learned behavior. elife 5.

Sutton RS, Barto AG, 2018. Reinforcement Learning: An Introduction. The MIT Press, Cambridge, Massachusetts, p. 526 (xxii).

Swanson LW, 1982. The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res. Bull 9, 321–353. [PubMed: 6816390]

Sweis BM, Larson EB, Redish AD, Thomas MJ, 2018. Altering gain of the infralimbic-to-accumbens shell circuit alters economically dissociable decision-making algorithms. Proc. Natl. Acad. Sci. USA 115, E6347–E6355. [PubMed: 29915034]

Tanji J, Hoshi E, 2001. Behavioral planning in the prefrontal cortex. Curr. Opin. Neurobiol 11, 164–170. [PubMed: 11301235]

Thompson BM, Baratta MV, Biedenkapp JC, Rudy JW, Watkins LR, Maier SF, 2010. Activation of the infralimbic cortex in a fear context enhances extinction learning. Learn. Mem 17, 591–599. [PubMed: 21041382]

Trask S, Thrailkill EA, Bouton ME, 2017. Occasion setting, inhibition, and the contextual control of extinction in Pavlovian and instrumental (operant) learning. Behav. Process 137, 64–72.

Tzschentke TM, Schmidt WJ, 1998. The development of cocaine-induced behavioral sensitization is affected by discrete quinolinic acid lesions of the prelimbic medial prefrontal cortex. Brain Res. 795, 71–76. [PubMed: 9622596]

Uylings HB, Groenewegen HJ, Kolb B, 2003. Do rats have a prefrontal cortex? Behav. Brain Res 146, 3–17. [PubMed: 14643455]

van Aerde KI, Heistek TS, Mansvelder HD, 2008. Prelimbic and infralimbic prefrontal cortex interact during fast network oscillations. PLoS One 3, e2725. [PubMed: 18628964]

Van den Oever MC, Rotaru DC, Heinsbroek JA, Gouwenberg Y, Deisseroth K, et al. , 2013. Ventromedial prefrontal cortex pyramidal cells have a temporal dynamic role in recall and extinction of cocaine-associated memory. J. Neurosci 33, 18225–18233. [PubMed: 24227731]

Vertes RP, 2004. Differential projections of the infralimbic and prelimbic cortex in the rat. Synapse 51, 32–58. [PubMed: 14579424]

Vidal-Gonzalez I, Vidal-Gonzalez B, Rauch SL, Quirk GJ, 2006. Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. Learn. Mem 13, 728–733. [PubMed: 17142302]

Villaruel FR, Martins M, Chaudhri N, 2021. Corticostriatal suppression of appetitive Pavlovian conditioned responding. J. Neurosci

Villaruel FR, Lacroix F, Sanio C, Sparks DW, Chapman CA, Chaudhri N, 2018. Optogenetic activation of the infralimbic cortex suppresses the return of appetitive pavlovian-conditioned responding following extinction. Cereb. Cortex 28, 4210–4221. [PubMed: 29045570]

Voorn P, Vanderschuren LJ, Groenewegen HJ, Robbins TW, Pennartz CM, 2004. Putting a spin on the dorsal-ventral divide of the striatum. Trends Neurosci 27, 468–474. [PubMed: 15271494]

Wang XJ, 2008. Decision making in recurrent neuronal circuits. Neuron 60, 215–234. [PubMed: 18957215]

Wang XJ, 2012. Neural dynamics and circuit mechanisms of decision-making. Curr. Opin. Neurobiol 22, 1039–1046. [PubMed: 23026743]

Warren BL, Mendoza MP, Cruz FC, Leao RM, Caprioli D, et al. , 2016. Distinct Fos-expressing neuronal ensembles in the ventromedial prefrontal cortex mediate food reward and extinction memories. J. Neurosci 36, 6691–6703. [PubMed: 27335401]

Warren BL, Kane L, Venniro M, Selvam P, Quintana-Feliciano R, 2019. Separate vmPFC ensembles control cocaine self-administration versus extinction in rats. J. Neurosci 39, 7394–7407. [PubMed: 31331999]

Willcocks AL, McNally GP, 2013. The role of medial prefrontal cortex in extinction and reinstatement of alcohol-seeking in rats. Eur. J. Neurosci 37, 259–268. [PubMed: 23106416]

Yin HH, Knowlton BJ, Balleine BW, 2004. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. Eur. J. Neurosci 19, 181–189. [PubMed: 14750976]

Young JW, Kerr LE, Kelly JS, Marston HM, Spratt C, et al. , 2007. The odour span task: a novel paradigm for assessing working memory in mice. Neuropharmacology 52, 634–645. [PubMed: 17097694]

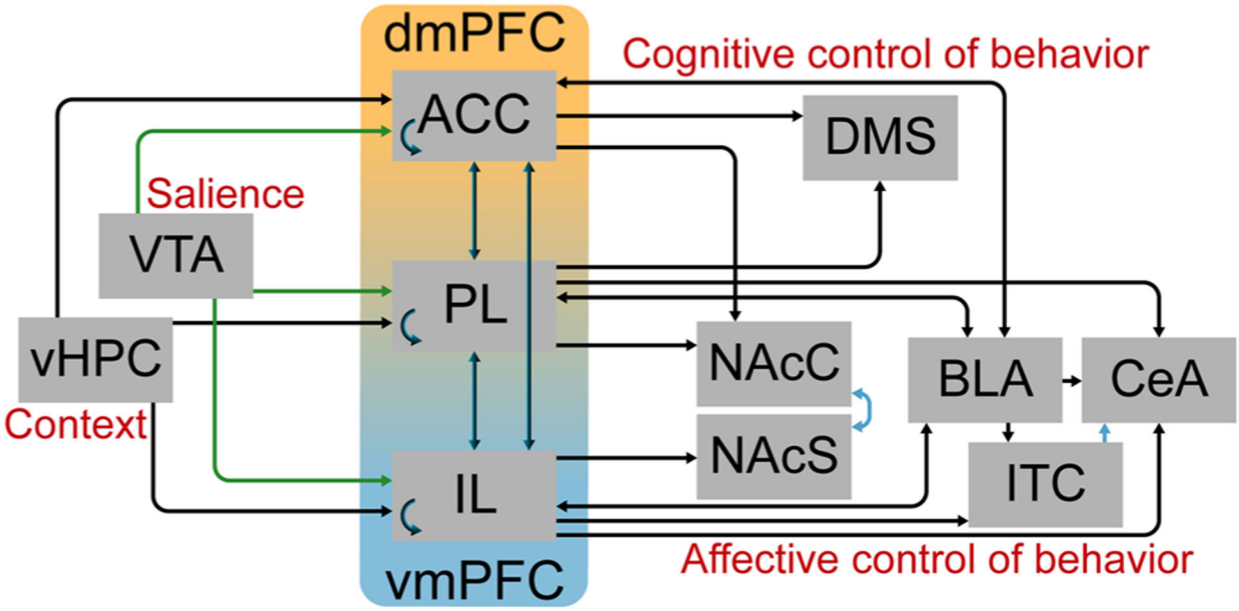

Fig. 1.

Schematic depicting the functional circuitry related to medial prefrontal cortex reviewed in the present manuscript. A brief description related to type of information or function of each circuit is included in red font. Glutamatergic projections are depicted in black, GABAergic projections in blue, and dopaminergic projections in green. Note that some arrows are black and blue to represent both glutamatergic and GABAergic projections between two areas.