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Dopamine tunes prefrontal outputs to orchestrate aversive processing

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Abstract

Decades of research suggest that the mesocortical dopamine system exerts powerful control over mPFC physiology and function. Indeed, dopamine signaling in the medial prefrontal cortex (mPFC) is implicated in a vast array of processes, including working memory, stimulus discrimination, stress responses, and emotional and behavioral control. Consequently, even slight perturbations within this delicate system result in profound disruptions of mPFC-mediated processes. Many neuropsychiatric disorders are associated with dysregulation of mesocortical dopamine, including schizophrenia, depression, attention deficit hyperactivity disorder, post-traumatic stress disorder, among others. Here, we review the anatomy and functions of the mesocortical dopamine system. In contrast to the canonical role of striatal dopamine in reward-related functions, recent work has revealed that mesocortical dopamine fine-tunes distinct efferent projection populations in a manner that biases subsequent behavior towards responding to stimuli associated with potentially aversive outcomes. We propose a framework wherein dopamine can serve as a signal for switching mPFC states by orchestrating how information is routed to the rest of the brain.

Keywords

Valence; Signal-to-noise ratio; Mesocortical; Aversion; Mesolimbic

1. Introduction to mesocortical dopamine

Dopamine is one of the most well-studied neurotransmitters in the brain and is primarily found in the nigrostriatal, tuberoinfundibular, mesolimbic, and mesocortical pathways (Björklund and Dunnett, 2007; Ikemoto, 2010). Mesencephalic, or midbrain, dopamine neurons innervate limbic and cortical areas through the mesolimbic and mesocortical pathways, respectively. A rich literature demonstrates the critical role of the mesolimbic

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pathway in reward-seeking, learning, and motoric function (Berridge and Robinson, 1998; Ikemoto, 2007; Wise, 2008). In contrast, the mesocortical dopamine system, which has been long-known to be a distinct and important population, has gained far less attention. Despite a relative paucity of investigations into mesocortical dopamine system function, studies consistently report that dysregulation of mesocortical dopamine underlies a wide array of pathologies found in neuropsychiatric disorders — including schizophrenia, depression, attention deficit hyperactivity disorder, and post-traumatic stress disorder (Arnsten and Dudley, 2005; Deutch and Young, 1995; Grace, 2016; Granon et al., 2000; Howes and Kapur, 2009; Lee et al., 2016; Lindström et al., 1999; Okubo et al., 1997; Pitman et al., 2012).

In preclinical literature, evidence supporting the idea that mesocortical dopamine is functionally distinct from mesolimbic dopamine dates back more than 40 years (Thierry et al., 1976). Early studies proposed the controversial theory that, in stark contrast to the well-documented role of mesolimbic dopamine in reward-related processes, mesocortical dopamine is primarily involved in encoding aversive events (Abercrombie et al., 1989; Mantz et al., 1989; Thierry et al., 1976). Over the last two decades, technical advances have greatly expanded our ability to assess the function of mesocortical dopamine circuits, and several groundbreaking studies definitively demonstrating a role of mesocortical dopamine in aversive processing have reinvigorated interest in this system (Gunaydin et al., 2014; Horvitz, 2000; Lammel et al., 2011, 2012).

Here, we review the evidence for mesocortical dopamine in aversion and highlight recent work that has begun to map out the complex actions of dopamine on diverse mPFC circuits. We outline a framework whereby mesocortical dopamine acts to amplify or dampen information streams within the mPFC to select the most appropriate information to be routed to downstream circuits.

2. Functions of the prefrontal cortex

To understand the activities of mesocortical dopamine, it is imperative to appreciate the functional and anatomical landscape in which it operates. The mPFC is a heterogeneous brain region implicated in a diverse range of cognitive and behavioral functions— including attention, decision-making, working memory, long-term memory, emotional control, inhibitory control, motivation, among many others (Bechara et al., 2000; Euston et al., 2012; Laubach et al., 2015; Miller, 1999; Ridderinkhof et al., 2004; Sawaguchi and Goldman-Rakic, 1991). While these functions may appear disparate, they all are related to cognitive control, or the ability to coordinate emotions and actions to support internally held goals (Miller, 2000; Miller and Cohen, 2001). Lesions of mPFC result in robust deficits in performance in tasks that require subjects to adapt their behavior across varying contexts, or tasks with dynamic or unexpected rules (Dias et al., 1996a, 1996b, 1997; Gehring and Knight, 2000; Gregoriou et al., 2014; Koenigs and Grafman, 2009; Milner, 1963; Rossi et al., 2007, 2009; Wilkinson et al., 1997). Thus, the mPFC appears to play a significant role in simultaneously inhibiting inappropriate behaviors, and promoting task- and contextually-relevant ones (Aron et al., 2004; Buschman and Miller, 2007; Dias et al., 1997; Thompson-Schill et al., 2002). Though many brain regions, neurotransmitter systems, and neural

circuits support goal-directed behavior, the mPFC is anatomically well-positioned to act as a hub that coordinates sensory inputs with internal states and goals to support adaptive behavioral outputs.

Successfully seeking rewards and avoiding punishments is critical for survival, and a defining characteristic of adaptive behavior. For these behaviors to occur optimally, neural systems must integrate internal motivational states with external information to orchestrate approach and avoidance of rewarding and aversive stimuli, respectively. Here we use rewarding or aversive stimuli as umbrella terms for stimuli that typically act as reinforcers or punishments in operant or place conditioning tasks, though we acknowledge that the response to many of these stimuli are dependent on a wide array of environmental factors. For example, an animal engaging in foraging behavior for food must constantly evaluate its environment for potential threats, which necessitate a transition from reward-seeking to threat avoidance. While the mPFC is not critical for basic stimulus-driven unconditioned behaviors, which are mediated by subcortical structures like the periaqueductal gray (Assareh et al., 2016; Bandler and Depaulis, 1988; Deng et al., 2016; Tovote et al., 2016) and hypothalamus (Anand and Brobeck, 1951; Bains et al., 2015; Betley et al., 2015; Burton et al., 1976; Jennings et al., 2015; Lin et al., 2011; Nieh et al., 2015, 2016), it plays a substantial role in deciphering ambiguous situations. In the example above, the foraging animal must not only perceive the environmental threat, but also evaluate its importance in relation to its ongoing efforts (e.g., How far away is the threat? How severe is the threat? How hungry am I? When will I be able to forage again?). In other words, the mPFC integrates sensory information with the perceived value of that information (i.e., how “good” or “bad” a stimulus is) together with internal belief states to provide top-down management of motivated behaviors.

There is substantial evidence supporting a crucial role of the mPFC in decision-making in the context of risk and reward, particularly in situations involving competition of appetitive and aversive drives — when both rewarding and aversive stimuli are simultaneously present (Bechara et al., 1994, 2005; Botvinick et al., 2004; Burgos-Robles et al., 2017; Mansouri et al., 2009; Milham et al., 2001). In rodents, pharmacological inactivation of the mPFC produces deficits in the coordination of reward-seeking and threat avoidance (Sangha et al., 2014; Sierra-Mercado et al., 2011). In humans, mPFC activity is modulated by the proximity of threat (Mobbs et al., 2007) suggesting a role in coordinating behavioral coping strategies. Not surprisingly, mPFC neuronal activity is robustly modulated by motivationally-relevant stimuli; including reward-delivery, reward-expectation, omission of reward, pain, and pain-predictive cues (Euston et al., 2012). Further, mPFC activity is highly correlated with aspects of reward- and fear-motivated behavioral output (Burgos-Robles et al., 2009, 2013). Thus, the mPFC has been metaphorically compared to a “switch operator” for sending trains down different tracks (Miller and Cohen, 2001), but the rules determining where information is sent, and the mechanisms for parsing information are still being discovered.

3. Anatomy of the prefrontal cortex

Consistent with the idea that the mPFC is crucial for cognitive control, this cortical region is most developed in primates and animals that have elaborate behavioral repertoires (Adolphs,

2009; Dunbar, 2009; Kerney et al., 2017; Noonan et al., 2018). In the rodent, the mPFC is often subdivided into four subregions – the secondary motor area (M2), the anterior cingulate cortex (ACC), the prelimbic cortex (PL), and infralimbic cortex (IL) – based on connectivity, cytoarchitectural, and functional differences (Heidbreder and Groenewegen, 2003; Ongür and Price, 2000) (Figure 1). A functional gradient along the dorsal-ventral axis of the mPFC (M2 > ACC > PL > IL) has been proposed, where more dorsal components control behavioral action and the more ventral components regulate emotions (Euston et al., 2012; Groenewegen and Uylings, 2000). M2 is the most dorsal of the mPFC regions and influences downstream circuits through inputs to motor regions and the spinal cord (Donoghue and Wise, 1982; Gabbott et al., 2005). While there is debate regarding the inclusion of M2 as a member of the mPFC family (Laubach et al., 2018), this premotor region is thought to link the evaluation of sensory information to motor outcomes (Barthas and Kwan, 2017). Adjacent to and ventral of M2 is the ACC, which is implicated in the error detection and evaluation of negative outcomes (Botvinick et al., 2004; Johansen and Fields, 2004; Shackman et al., 2011). In line with these theories, the ACC is robustly activated in response to pain and pain-predictive stimuli (Allsop et al., 2018; Frankland et al., 2004; Vogt, 2005). Finally, the PL and IL areas comprise the ventral medial aspects of the mPFC and are strongly interconnected to both limbic and autonomic control centers (Gabbott et al., 2005; Heidbreder and Groenewegen, 2003; Vertes, 2004). Further, these regions appear to be crucial for the detection, monitoring, and updating of instrumental contingencies (Cardinal et al., 2002). Together, this collection of mPFC nuclei access motivationally-relevant and homeostatic information to guide adaptive, goal-directed behaviors via input to emotional, autonomic, and motor loci.

The mPFC consists of diverse cell types. The neuronal cell types are broadly split into excitatory, glutamatergic pyramidal cells, and inhibitory GABAergic interneurons, which represent ~80–90% and 10–20% of the population, respectively (Gabbott et al., 1997, 2005). Traditionally, it has been thought that pyramidal neurons comprise the entirety of the long-range projection neurons in the mPFC while GABAergic interneurons powerfully regulate their activity via dense local connectivity (Isaacson and Scanziani, 2011). However, recently long-range GABAergic projections targeting the nucleus accumbens (NAc) have also been described (Lee et al., 2014). Both pyramidal and interneuron populations contain many subclasses distinguished by their functional, laminar, morphological, electrophysiological, and molecular properties (Gabbott et al., 1997, 2005; Kvitsiani et al., 2013; Markram et al., 2004). Overall, the delicate balance of these excitatory and inhibitory forces (i.e., “E/I balance”) within the mPFC are crucial for optimal cognitive performance (Rubenstein and Merzenich, 2003; Yizhar et al., 2011).

Similar to other cortical structures, the mPFC is laminarily organized (Douglas and Martin, 2004; Gabbott et al., 2005; Kritzer and Goldman-Rakic, 1995). The mPFC receives diverse sensory and limbic afferent connections (Hoover and Vertes, 2007) arriving predominantly in superficial Layers 1 and 2/3 (Douglas and Martin, 2004; Romanski et al., 1999a, 1999b). mPFC efferent connections are equally robust, projecting to cortical and subcortical brain regions (Gabbott et al., 2005; Groenewegen et al., 1997; Heidbreder and Groenewegen, 2003; Sesack et al., 1989; Vertes, 2004). Long-range efferent cortical-subcortical projections originate mainly from the deep layers (Layer 5 and Layer 6), while cortical-cortical

projections arise primarily from superficial Layer 2/3 (DeFelipe and Fariñas, 1992; Douglas and Martin, 2004; Gabbott et al., 2005). Notably, efferent connections appear to be densest to regions involved in emotional and autonomic control— including the amygdala, ventral striatum, insula, hypothalamus, periaqueductal gray, habenula, and midline thalamic structures (Gabbott et al., 2005; Groenewegen et al., 1997; Heidbreder and Groenewegen, 2003; Sesack et al., 1989; Vertes, 2004). Through this dense interconnectivity, the mPFC is thought to exert executive, top-down control over processing of rewarding and aversive events, as well as subsequent emotional regulation and control of actions. However precise, causal investigations into the potentially distinct functions of mPFC output populations are still lacking. It is unclear how mPFC parses incoming information, how this information is divided between outputs, and how these projections are influenced by dopamine.

4. Midbrain dopamine neurons

The mPFC has reciprocal connectivity with several neuromodulatory systems known to be involved in adaptive responses to rewarding and aversive events— including the midbrain dopamine system (Christie et al., 1985; Gabbott et al., 1997; Heidbreder and Groenewegen, 2003; Tye et al., 2013; Warden et al., 2012). The two largest dopaminergic nuclei are the ventral tegmental area (VTA, also known as A10) and substantia nigra pars compacta (SNc, also known as A9) (Björklund and Dunnett, 2007), which are both anatomically and functionally distinct populations. While VTA dopamine neurons regulate motivation and encode reward expectation, substantia nigra neurons are more involved in motor functions via connections to the dorsal striatum / caudate putamen (Berridge and Robinson, 1998; Björklund and Dunnett, 2007; Michel et al., 2016; Phillips et al., 2003; York, 1973). In the rodent brain, VTA dopamine neurons send dense projections to the ventral striatum (including the NAc) and sparser projections to the mPFC, amygdala, and hippocampus (Haber and Fudge, 1997) (Figure 1a). However, it is important to note that there is considerable variation across mammalian species. For example, dopaminergic innervation of the cortex is much denser in primates (Bentivoglio and Morelli, 2005; Descarries et al., 1987; Lewis and Sesack, 1997; Thierry et al., 1973) and appears to be more homogenous across cortical layers (Berger et al., 1991; Williams and Goldman-Rakic, 1993; Vander Weele et al., 2018).

VTA dopamine neurons transmit signal in two modes: 1) “Tonic” mode is characterized by a consistent, pacemaker-like 2–5 Hz firing rate, and 2) “Phasic” mode is characterized by transient bursts of high frequency 10–20+ Hz firing lasting 100–500 ms (Bunney et al., 1991; Grace and Bunney, 1984a, 1984b; Grace et al., 2007). The net effect of tonic firing/ release, reuptake, diffusion and degradation mechanisms result in a relatively stable basal, extracellular level of dopamine, or tonic dopamine, in downstream targets (Cragg and Rice, 2004; Ferris et al., 2014). Phasic VTA dopamine neuron firing rapidly and transiently increases dopamine levels, estimated to reach levels of ~100 μ M in striatal synapses (Garris and Wightman, 1994; Grace et al., 2007) (Garris and Wightman, 1994; Grace et al., 2007), termed ‘phasic dopamine release’ or dopamine ‘transients’ (Robinson et al., 2003). Both tonic dopamine level and phasic release modulate the activity of specific populations of neurons expressing postsynaptic dopamine receptors (see below for more detailed discussion) (Dreyer et al., 2010, 2016; Owesson-White et al., 2016). It is thought that the

impact of phasic dopamine transients are determined by the size of the transient relative to the basal level of dopamine present in that microdomain (Wanat et al., 2009), making the interplay between tonic and phasic dopamine a critical determinant of the impact of dopamine cell firing. To make matters more complicated, action potential bursts at the dopamine cell bodies do not always translate to phasic release events downstream. Indeed, dopamine levels in striatum and cell firing of dopamine neurons in the VTA are often decoupled (Mohebi et al., 2018; Trulson, 1985), which is a result of the fact that dopamine terminal activity is heavily influenced by a number of mechanisms including input from local interneurons and a wide array of presynaptic modulatory receptors, such as dopamine autoreceptors (Cachope and Cheer, 2014; Cachope et al., 2012; Cragg and Rice, 2004; Dreyer and Hounsgaard, 2013; Zhang and Sulzer, 2004). As such, it is important to use multidisciplinary approaches to appreciate the complex and dynamic interactions between somatic activity, dopamine release, reuptake, and local modulatory mechanisms.

Dopamine release and reuptake dynamics and their postsynaptic actions have been studied in detail within the striatum, but the extent to which these principles translate to other brain regions which receive dopaminergic afferents, like the mPFC, is unclear. Certainly there are some significant differences. For example, in contrast to tight reuptake regulation in the striatum, dopamine neurotransmission in the mPFC is not as temporally controlled. In the striatum, the dopamine transporter (DAT) dictates the duration of dopamine's actions in the synapse and the extent to which it diffuses (Cragg and Rice, 2004). In the mPFC, dopamine axons largely lack DAT immunoreactivity (Sesack et al., 1998) which results in reduced reuptake and greater extracellular diffusion distances (Cass and Gerhardt, 1995; Garris and Wightman, 1994; Garris et al., 1993; Vander Weele et al., 2018). Evidence suggests that dopamine clearance is mediated in part by the norepinephrine transporter (NET) (Carboni et al., 1990; Miner et al., 2003; Sesack et al., 1998; Tanda et al., 1994). However, NET immunoreactivity is sparse in the deep layers of the mPFC and recordings of dopamine neurotransmission show temporally prolonged signals indicative of reduced capacity for clearance (Garris and Wightman, 1994; Garris et al., 1993; Vander Weele et al., 2018). Thus dopamine release in the deep layers of the mPFC appears to be primarily regulated by extraneuronal metabolism (Karoum et al., 1994; Maisonneuve et al., 1990; Sharp et al., 1986), an enzymatic degradation process that is slower than the fast protein-mediated reuptake. Considering this, caution should be used when comparing dopamine dynamics and functions between the striatum and the mPFC as the results may not be generalizable.

Phasic dopamine neuron activity and phasic dopamine release have been studied extensively in the context of reward (Covey et al., 2014; Tsai et al., 2009; Wanat et al., 2009; Wickham et al., 2013), and to a lesser extent, aversion (Badrinarayan et al., 2012; Budygin et al., 2012; Wenzel et al., 2015). In a seminal study by Schultz and colleagues (1997), dopamine neurons were found to change their activity based on reward expectation: dopamine neurons increased their firing to unexpected reward delivery, but shifted this response to cues that predict reward delivery after pairing— which is reflected in ventral striatal phasic dopamine release (Day et al., 2007). VTA dopamine neurons also exhibited a decrease in firing if an expected reward (i.e., predicted by a conditioned stimulus) was omitted (Schultz et al., 1997). Further, some studies report inhibition of dopamine activity in response to aversive events or conditioned stimuli that predict them (Badrinarayan et al., 2012; Oleson et al.,

2012; Roitman et al., 2008; Twining et al., 2015; Ungless et al., 2004; Wheeler et al., 2011). Finally, by optogenetically activating dopamine neurons at the time of reward receipt, motivational value can be attributed to neutral cues, even in the absence of error, demonstrating causality between dopamine neuron activation and Pavlovian conditioning of antecedent cues (Steinberg et al., 2013). Together, these neurons have been described as encoding “reward prediction error” (RPE) by signaling discrepancies between expected and actual outcomes. As such, RPEs provide a mechanism for learning the outcomes of predictive stimuli and updating their internal representations when the magnitude, valence, or timing of predicted outcomes differs from expectation.

RPE theory is largely based on observing the endogenous action potential activity of midbrain dopamine neurons, many of which project to the ventral striatum, and by observing dopamine transients in the ventral striatum. While the majority of dopamine neurons in the midbrain have activity profiles that appear consistent with RPE theory, there are also small subpopulations that are not consistent, such as cells that show phasic responses to aversive stimuli (Brischoux et al., 2009, 2009; Mantz et al., 1989; Matsumoto and Hikosaka, 2009; Matsumoto et al.). These findings have sparked considerable debate over dopamine’s role in processing of aversive events. As previously mentioned, several theories have suggested that phasic dopamine responses primarily encode reward-related events— including food reward, water reward, social targets, sex, and drugs of abuse (Covey et al., 2014; Robinson et al., 2003). However, dopamine responses to various salient and aversive stimuli — including surprising events, stress, pain, and fear-predictive cues have also been reported (Abercrombie et al., 1989; Badrinarayan et al., 2012; Budygin et al., 2012; Matsumoto and Hikosaka, 2009; Matsumoto et al.; McCutcheon et al., 2012; Salamone, 1994; Wenzel et al., 2015). As a result, new theories of dopamine function have suggested roles in alerting (Bromberg-Martin et al., 2010), invigoration of ongoing behaviors (Niv, 2007; Salamone et al., 2007; da Silva et al., 2018), or encoding the value of work (Berke, 2018; Hamid et al., 2016).

In addition to the VTA and SNc, there are several other dopaminergic nuclei scattered throughout the brain. One population of interest is dopamine neurons located in the dorsal raphe nucleus (DRN), an area traditionally known for being the primary source of serotonin in the brain, which recently have also been implicated in the processing of salient stimuli (Cho et al., 2017; Li et al., 2016; Matthews et al., 2016). Activation of DRN dopamine neurons promotes avoidance in real-time and conditioned place-preference assays suggesting that activity within this population is aversive (Matthews et al., 2016). DRN dopamine neurons send ascending projections primarily to the central nucleus of the amygdala (CeA) and the bed nucleus of the stria terminalis (BNST) (Li et al., 2016; Matthews et al., 2016). Additionally, functionally distinct populations within the VTA and substantia nigra continue to be discovered. For example, a recent set of studies identified a group of dopamine neurons projecting from the substantia nigra pars lateralis to a long-overlooked region in the caudal most extent of the striatum, called the tail of the striatum (Menegas et al., 2015). This population encodes the perceived threat of stimuli, and reinforces retreat behaviors (Menegas et al., 2015). The increasing evidence for heterogeneity within and between dopamine neuron populations in the processing of

rewarding and aversive stimuli call for more precise interrogations into their cognitive and behavioral operations.

5. Characteristics of the mesocortical dopamine pathway

How is dopamine involved in so many seemingly disparate processes? Over the last two decades it has become increasingly clear that VTA dopamine neurons form subpopulations with heterogeneous functions, which are, at least in part, defined by their disparate projection targets (Bromberg-Martin et al., 2010; Kim et al., 2016a; Lammel et al., 2014). For example, VTA dopamine neurons that project to the NAc appear to be involved in different operations than those projecting to the mPFC, amygdala, and hippocampus. This notion of defining subpopulations of dopamine neurons by their anatomy (e.g., “projection-defined”) is supported by the finding that the majority of VTA dopamine neurons do not collateralize. Current evidence suggests that they send independent, non-overlapping ascending projections to target regions (Albanese and Minciacchi, 1983; Breton et al., 2018; Chandler et al., 2013; Fallon, 1981). Further, these projection-defined VTA dopamine subpopulations maintain several distinct features, including receptor expression (Bannon and Roth, 1983; Bannon et al., 1981; Lammel et al., 2008), electrophysiological properties (Chiodo et al., 1984; Lammel et al., 2008), anatomical location (Lammel et al., 2012) (Figure 1b), afferent connectivity (Lammel et al., 2012), and responses to stimuli with positive or negative valence (Abercrombie et al., 1989; Bassareo et al., 2002; Kim et al., 2016a; Lammel et al., 2011; Mantz et al., 1989). (Figure 2). Accordingly, growing evidence supports distinct behavioral roles of VTA dopamine subpopulations depending on their forebrain projection target.

In rodents, although dopaminergic terminals in the mPFC are relatively sparse (Descarries et al., 1987) and correspondingly, dopamine release is lower compared to other forebrain regions, such as the NAc (Garris and Wightman, 1994; Garris et al., 1993), motivationally-relevant stimuli robustly modulate dopamine neurotransmission in the mPFC (Abercrombie et al., 1989; Bassareo et al., 2002; Finlay et al., 1995; Hernandez and Hoebel, 1990), which profoundly impacts mPFC activity (Arnsten, 1997; Berridge and Arnsten, 2013; Decot et al., 2017; Seamans and Yang, 2004; Sesack and Bunney, 1989). Measurements of neurotransmitter release and neuronal activity show the mPFC dopamine pathway is activated by both rewarding (Ahn and Phillips, 1999; Bassareo et al., 2002; Ellwood et al., 2017; St Onge et al., 2012) and aversive stimuli (Finlay et al., 1995, 1995; Kim et al., 2016a; Lammel et al., 2011; Mantz et al., 1989; Thierry et al., 1976). However, several studies have suggested that the mPFC dopamine system is preferentially sensitive to aversive events.

An important series of studies by Lammel and colleagues demonstrated that projection-defined VTA dopamine neurons differentially respond to rewarding and aversive stimuli. More specifically, these studies have suggested that VTA dopamine neurons projecting to the NAc encode aspects of reward or reinforcement, while VTA dopamine neurons projecting to the mPFC may encode aspects of aversion (Lammel et al., 2011, 2012). First, Lammel and colleagues (2011) showed that enhanced synaptic plasticity onto VTA dopamine neurons following rewarding and aversive events depends on projection-defined subpopulations. *In vitro* AMPA/NMDA ratios, as a measure of synaptic strength, are enhanced in VTA

dopamine neurons projecting to the NAc medial shell after cocaine experience – a highly rewarding and reinforcing experience (Deroche et al., 1999; Nomikos and Spyraki, 1988; Roberts et al., 1977). In contrast, aversive stimulus experience — formalin injection into the paw (Dubuisson and Dennis, 1977) – did not change AMPA/NMDA in NAc medial shell-projecting VTA dopamine neurons. The opposite pattern of results was observed in VTA dopamine neurons projecting to the mPFC: synaptic plasticity was enhanced following aversive experience but not after rewarding experience (Lammel et al., 2011).

Direct measurements of dopamine activity have also revealed activation of the mesocortical pathway in response to noxious stimuli. In an early, influential *in vivo* microdialysis study, Abercrombie and colleagues showed that dopamine in the mPFC is robustly elevated following tail pinch compared to dopamine levels in the dorsal and ventral portions of the striatum, despite significantly denser striatal innervation (Abercrombie et al., 1989). Within the VTA, *in vivo* electrophysiological recordings of putative mPFC- and NAc-projecting dopamine neurons revealed preferential responsivity of the mesocortical pathway to tail pinch – with 65% exhibiting excitation and 25% inhibition – whereas NAc-projecting units were largely non-responsive (Mantz et al., 1989). More recently, bulk calcium signals from dopaminergic axon terminals recorded simultaneously in the mPFC and NAc with *in vivo* fiber photometry show divergent responsivity to rewarding and aversive stimuli (Kim et al., 2016). Here, VTA dopamine terminals in the NAc were activated by water reward and inhibited by tail shock, whereas terminals in the mPFC were activated by tail shock and not robustly modulated by water reward (Kim et al., 2016).

While microdialysis and photometry studies have been used to make critical discoveries regarding the function of mesocortical dopamine, these methods are limited in several important ways (for review, Wickham et al., 2013). Microdialysis provides a direct measure of dopamine release, but is limited in temporal resolution as samples are collected every on the order of minutes. Photometry has temporal resolution in the low seconds range, closer to that of real-time dopamine signaling, but is an indirect, proxy measure of dopamine release. The most direct way of monitoring real-time phasic dopamine release is fast-scan cyclic voltammetry (FSCV), which has been used with great success in dopamine-rich areas such as the striatum, but has proven difficult to implement in the mPFC. Indeed, while FSCV offers a direct measurement of catecholamine neurotransmission with precise temporal resolution, it is rarely used outside the NAc (but see: Garris and Wightman, 1994; Garris et al., 1993; Matthews et al., 2016) due to difficulty in discriminating between norepinephrine and dopamine (Heien et al., 2003) as well as relatively poor sensitivity – which has limited its application in brain regions like the mPFC which receive both dopaminergic and noradrenergic innervation (Figure 1a), and also have much lower magnitude dopamine release events. Thus, the time course and source of dopamine release in the mPFC upon aversive stimuli presentation has been difficult to parse with this method, and instead has been inferred from less direct approaches. Recently however, we used optogenetic and pharmacological methods to identify the source of dopamine release in the mPFC in response to tail pinch. Consistent with previous studies, we found that tail pinch produces rapid elevations in catecholamine release that are time-locked to its onset (Vander Weele et al., 2018), particularly in the deep layers of the mPFC where dopamine terminals are the densest relative to norepinephrine terminals (Figure 1c). Considering optogenetic inhibition

of VTA dopamine neurons attenuated tail pinch evoked release, and that pharmacological inactivation of norepinephrine neurons in the locus coeruleus did effect responses to tail pinch (Vander Weele et al., 2018), these findings strongly suggests that this catecholamine signal is dopaminergic and arises from VTA dopamine neurons.

While several reports have convincingly demonstrated that mesocortical dopamine is preferentially responsive to aversive stimuli, this conclusion does not resolve all of the empirical data. Indeed, several microdialysis studies have reported enhancements in extracellular dopamine release in the mPFC following exposure to rewarding stimuli, specifically food consumption (Ahn and Phillips, 1999; Bassareo et al., 2002; Hernandez and Hoebel, 1990; St. Onge et al., 2012). Recently, phasic dopamine responses were reported from VTA dopamine terminals in the mPFC in response to reward, measured by *in vivo* fiber photometry (Ellwood et al., 2017). Here they observed an increase in axonal calcium signals from VTA dopamine terminals in the mPFC in response to reward-predictive cues and reward-delivery (Ellwood et al., 2017), reminiscent of dopamine transients observed in the NAc using *in vivo* fast-scan cyclic voltammetry during a similar Pavlovian conditioning paradigm (Day et al., 2007). These data suggest that dopamine neurotransmission in the mPFC may play a role in reward-related processes. However, non-psychostimulant addictive drugs (e.g., morphine, ethanol, nicotine) do not enhance dopamine release in the mPFC (Bassareo et al., 1996), despite their rewarding and reinforcing properties. Further, drugs that enhance dopamine concentrations in the mPFC (e.g., antidepressants) are not typically substances of abuse (Tanda et al., 1994), suggesting that dopamine in mPFC has a differential role in reward and reinforcement as compared to accumbal dopamine. While distinct from mesolimbic dopamine, mesocortical dopamine still plays an important role in self-administration of abused compounds. Indeed, destruction of dopamine terminals in the mPFC increases motivation to self-administer cocaine in rats (McGregor et al., 1996), and micro-infusions of cocaine into the mPFC are capable of maintaining self-administration (Goeders and Smith, 1983). Reconciling these findings is difficult for several reasons including the disparate time scales over which dopamine has been recorded (e.g. FSCV versus microdialysis), and the fact that many studies only assessed the effects of either an aversive or rewarding stimuli rather than comparing between the two. Indeed Ellwood and colleagues (2017) did not also investigate dopamine responsivity to aversive stimuli, omission of reward, or under competitive situations. It remains possible that dopamine optimizes prefrontal functions in each given context and that aversive stimuli represent a robust strategy-switching signal that is reflected in the mesocortical dopamine pathway's sensitivity to aversive events. Another potential explanation is that mesocortical dopamine is preferentially responsive to aversive stimuli on a short, second to second timescale, but is elevated by rewarding stimuli over longer periods of time. Additional studies will be needed to fully resolve this important discrepancy in the extant literature.

The idea that mesocortical dopamine is preferentially sensitive to aversive stimuli has been proposed several times to be a unique feature of this population, but largely has not been incorporated into overarching models and theories of mesocortical dopamine function. In a second study by Lammel and colleagues (2012) they show that activation of inputs onto VTA neurons projecting to either NAc or mPFC with optogenetics resulted in reinforcement

and aversion, respectively. Further, direct activation of VTA dopamine terminals has been shown to support conditioned place avoidance and promote anxiety-related behavior (Gunaydin et al., 2014), while destruction of dopaminergic innervation of the mPFC disrupts escape behavior (Sokolowski et al., 1994). Yet the role of mesocortical dopamine in aversive motivation remains controversial. For example, in stark contrast to the initial reports by Gunaydin and colleagues (2014), two recent studies showed no effect of optical activation of VTA dopamine axon terminals on place preference (Ellwood et al., 2017, Vander Weele et al., 2018). These seemingly contradictory reports fail to provide a cohesive understanding of the functional role of dopamine in the mPFC.

Positive and negative cues that guide motivated behaviors rarely exist in isolation outside of the laboratory. In naturalistic settings, stimuli that predict rewards and punishments coexist and the mPFC evaluates the probability of their outcomes in order to guide adaptive behavior. However, few preclinical studies have explored dopaminergic modulation of competitive situations. Dopaminergic modulation of mPFC activity may have profound behavioral impact considering the importance of mPFC in higher-order cognition, decision-making and evaluation of uncertain situations (Floresco, 2013; Floresco and Magyar, 2006; Ragozzino, 2002). Recently, a behavioral assay was developed to examine the role of mesocortical dopamine during conflicting Pavlovian associations (Burgos-Robles et al., 2017). In this assay, rats learned to discriminate between sucrose- and footshock-predictive cues, resulting in approach to the reward delivery port and freezing, respectively. After learning, conflict was introduced by simultaneously presenting the two stimuli to induce an intermediate behavioral phenotype – characterized by within- and between-subject individual differences in sucrose port approach and freezing behavior. Optogenetic activation of VTA dopamine terminals in the mPFC during these competition trials biased behavior towards freezing at the expense of port approach and sucrose consumption (Vander Weele et al., 2018). These data suggest that under certain conditions, the sensitivity of the mesocortical system to aversive stimuli may tune mPFC circuits to promote avoidance or escape behaviors, and may help to explain the variability across studies in the ability of dopamine in the mPFC to directly condition aversive responses.

6. Valence routing by prefrontal projections

It is still unknown if neural responses in mPFC carrying information of competing valences can be mapped onto specific output circuits, what modulates their competitive interactions, and how competing information streams ultimately win control of behavioral outputs. Further, considering mPFC neurons are responsive to both rewarding and aversive stimuli (Burgos-Robles et al., 2009, 2013; Euston et al., 2012), it is possible that mPFC neuronal circuits encoding aversive or rewarding events are differentially modulated by dopamine, resulting in a vast array of computations and behavioral outcomes. As previously mentioned, subcortical projection predominately reside in output Layers 5 and 6 (Gabbott et al., 2005), which also express dopamine receptors (Gaspar et al., 1995). Prominent projections from the mPFC include the: basolateral amygdala, NAc / ventral striatum, lateral hypothalamus, periaqueductal gray, medial dorsal thalamus, and paraventricular nucleus of the thalamus (Gabbott et al., 2005; Vertes 2004). Here we highlight a subset of projection-defined mPFC

subpopulations implicated in motivated behaviors in response to rewarding and aversive stimuli.

mPFC-NAc

The NAc is historically viewed as a reward center because of its involvement in reward-learning (Day and Carelli, 2007; Day et al., 2007), reward-seeking (Phillips et al., 2003) and hedonic pleasure (Castro and Berridge, 2014). mPFC projections to the NAc comprise ~27% of Layer 5 pyramidal neurons and ~13% of superficial Layer 2/3 (Gabbott et al., 2005). Optogenetic stimulation of mPFC terminals in the NAc has been shown to support place preference and operant reinforcement in some (Britt et al., 2012), but not in all studies (Otis et al., 2017; Stuber et al., 2011, Vander Weele et al., 2018) – perhaps due to location of stimulation (i.e., soma versus terminal) or stimulation parameters (i.e., frequency, light power). Recently, *in vivo* cellular resolution calcium imaging of mPFC-NAc neurons during reward-learning has revealed enhanced responses to reward-predictive cues during conditioning in this pathway (Otis et al., 2017), consistent with previous reports (Ishikawa et al., 2008). Given that optogenetic stimulation promotes the expression of conditioned-reward-seeking (Otis et al., 2017), current evidence ties the excitatory mPFC-NAc pathway to orchestrating components of reward-learning and seeking. Recently, the mPFC-NAc pathway has proven to demonstrate combined coding for social rewards, representing both social and spatial coding (Murugan et al., 2017). These studies suggest that the mPFC-NAc projection may represent diverse features about cues and contexts related to reward.

mPFC-PAG

The PAG is also innervated by mPFC, but this population of mPFC output neurons is functionally and anatomically distinct (Vander Weele et al., 2018) from those that project to the NAc. The PAG is a midbrain structure considered an important relay center for information regarding threatening stimuli and subsequent defensive responses (Bandler and Carrive, 1988; Bandler and Depaulis, 1988; Bandler et al., 1985; Fanselow, 1991; Tovote et al., 2016). In humans, the PAG is implicated in mediating negative affective states and processing of aversive events (Buhle et al., 2013; Satpute et al., 2013; Young et al., 1985), threat proximity (Canteras and Graeff, 2014; Mobbs et al., 2007, 2010), threat anticipation (Meyer et al., 2017), and escape (Evans et al., 2018). In non-human primates, local electric and glutamate stimulation of the PAG elicits a diverse range of aversive and defensive behavioral reactions, which are topographically segregated in subcolumns along both medial-lateral and dorsal-ventral axes (Bandler and Depaulis, 1988; Deng et al., 2016). mPFC projections to the PAG comprise ~3% of Layer 5 pyramidal neurons (Gabbott et al., 2005) and innervate both dorsal (dPAG) and ventral (vPAG) subregions. mPFC projections to the dPAG are comprised entirely of glutamatergic neurons, and synapse on glutamatergic neurons in the dPAG (Franklin et al., 2017). Although the genetic identity of mPFC projections to the vPAG have not been explored, the ventral and dorsal subregions are known to regulate distinct fear-related operations. Indeed, while the dPAG orchestrates active threat avoidance strategies (i.e., escape), the vPAG promotes passive coping strategies (i.e., freezing) (Bandler and Carrive, 1988; Deng et al., 2016; Halladay and Blair, 2015; Tovote et al., 2016). These functional distinctions also appear to be reflected in cortical input to PAG subregions along the dorsal-ventral axis. Optogenetic activation of the mPFC-dPAG pathway

specifically supports conditioned and real-time place aversion / avoidance and promotes marble burying (Vander Weele et al., 2018), a defensive behavior in rodents in response to localizable threats (De Boer and Koolhaas, 2003). In contrast, the mPFC projections to vPAG mediate aspects of contextual fear conditioning and discrimination (Rozeske et al., 2018). Together these data strongly suggest that the mPFC projections to the PAG mediated various coping strategies in response to aversive stimuli.

mPFC-thalamus

The mPFC also has dense reciprocal connectivity with medial dorsal thalamic nuclei (Collins et al., 2018; Gabbott et al., 2005; Ray and Price, 1993; Schmitt et al., 2017), which are anatomically distinct from other mPFC outputs (Otis et al., 2017). Thalamic projections arise predominately from deep layer 6, comprising almost half of Layer 6 pyramidal neurons (Gabbott et al., 2005). While mPFC neurons innervate various thalamic structures, two downstream targets of interest are the mediodorsal thalamus (MD) and periventricular nucleus of the thalamus (PVT). Similar to projections to NAc and PAG, mPFC projections to the PVT have been implicated in valence processing. Do-Monte and colleagues (2015) have shown that during late-stage fear memory retrieval, mPFC projections to PVT are activated, and that this activity is necessary for fear memory retrieval (Do-Monte et al., 2015). Complimentary findings have demonstrated that this circuit is tuned during reward learning such that reward-predictive cues elicit inhibitory responses, which may be permissive to the expression of cued reward seeking (Otis et al., 2017). Accordingly, optogenetic activation of mPFC projections to the PVT time-locked to the presentation of a reward-predictive cue blocks both the acquisition and expression of conditioned reward-seeking. Given that activation of mPFC-PVT neurons does not support real-time place preference or aversion (Otis et al., 2017), these data implicate this pathway in mediating conditioned/learned, rather than unconditioned/innate motivated behaviors. Connections between the mPFC and the thalamic nucleus reuniens (RE) are involved in the extinction of Pavlovian fear memories and appear to inhibit the expression of fear (Ramanathan et al., 2018). While there is rich preclinical literature exploring MD inputs to the mPFC, particularly in the context of working memory and behavioral flexibility (Bolkan et al., 2017; Schmitt et al., 2017; Wimmer et al., 2015), there have been considerably less functional investigations in the reciprocal direction (but see: Marton et al., 2018). Considering the density of the mPFC-MD pathway and its association with neuropsychiatric disorders (George et al., 2001; Greicius et al., 2007), exploration into its role in processing of rewarding and aversive stimuli could be an interesting avenue for future research.

mPFC-BLA

Connections between the mPFC and BLA have received significant attention (Adhikari et al., 2015; McGarry and Carter, 2017; Murugan et al., 2017; Sotres-Bayon and Quirk, 2010; Yizhar and Klavir, 2018), given the BLA's role in processing salient and valence-defined stimuli (Janak and Tye, 2015; Namburi et al., 2015; Shabel and Janak, 2009). mPFC neurons projecting to the BLA originate in both Layer 2/3 (10% of Layer 2/3 pyramidal neurons) and Layer 5 (8% of Layer 5 pyramidal neurons (Gabbot et al., 2005). mPFC-BLA projectors appear to be anatomically distinct from other projector populations (Murugan et al., 2017), but there is evidence of collateralization (Vander Weele et al., 2018). This circuit has been

implicated in mediating components of aversive behaviors, including forms of fear-learning (Allsop et al., 2018; Karalis et al., 2016), fear-extinction (Adhikari et al., 2015; Bukalo et al., 2015), anxiety (Adhikari et al., 2015), and innate threat responses (Jhang et al., 2018) (for review, Rozeske and Herry, 2018; Sotres-Bayon and Quirk, 2010). Indeed, theta oscillations in this pathway have been casually linked to the expression of fear-behavior (Karalis et al., 2016). However, it is important to appreciate the heterogeneity across prefrontal subregions in regard to the function of their projections to the BLA. For example, Adhikari and colleagues (2015) show that dorsal and ventral mPFC neurons projecting to BLA differentially regulate conditioned fear responses and anxiety. Here they demonstrate that ventral mPFC-BLA inhibits fear- and anxiety-related behaviors, while dorsal mPFC-BLA promotes anxiety (Adhikari et al., 2015). Although beyond the scope of this review, reciprocal projections also exist from the BLA to the mPFC (Burgos-Robles et al., 2017; Felix-Ortiz et al., 2016; McGarry and Carter, 2017).

Diversity also exists within other prefrontal circuits – ACC projections to the BLA are implicated in both innate threat responses and socially transmitted fear learning, but seem to be less involved in classically conditioned fear responses (Burgos-Robles et al., 2017; Felix-Ortiz et al., 2016; McGarry and Carter, 2017). Functional heterogeneity based on projection origin within the mPFC subregions likely extend to other mPFC output populations (i.e., mPFC-PAG, mPFC-NAc), but largely have not been parsed to this level of granularity. Overlaying the functional aspects of defined mPFC circuits on the dorsal-ventral axis of the mPFC will be an important future direction.

Other mPFC circuits

The mPFC contains several other projection-defined and local subpopulations that may be responsible for differential routing of reward and aversive information. For example, the pathway between the mPFC and dorsal raphe nucleus (DRN) is involved in the selection and activation of coping behaviors in the face of threat (Baratta et al., 2009; Warden et al., 2012), but further investigation of this pathway in both reward and aversive contexts is required. Additionally, while the lateral hypothalamus has been implicated in both aversive and appetitive behaviors, the role of input from the mPFC has not yet been thoroughly interrogated, despite relatively dense connectivity (Gabbott et al., 2005). Finally, active avoidance requires inhibitory signaling in the mPFC (Diehl et al., 2018) and a subsets of local inhibitory cells have also been shown to be important for fear responses (Courtin et al., 2014; Sparta et al., 2014). Yet understanding how these local microcircuits interface with specific projections, and how dopamine may regulate these interactions to modulate their behavioral outcomes remains an ongoing effort.

7. Dopaminergic mechanisms of action and circuit modulation in the mPFC

One difficulty in unraveling the mystery of dopamine's actions in the prefrontal cortex is in simply determining the post-synaptic actions of dopamine on mPFC neurons. This is a particularly complex issue compared to the well-documented effects of dopamine on principle neurons in the striatum. In the striatum, D1 and D2-type dopamine receptors

(based on mRNA expression) are expressed on almost entirely non-overlapping populations of medium spiny neurons, the primary output neuron of the striatum which account for more than 95% of total striatal neurons (Gerfen and Surmeier, 2011; Tepper et al., 2008). Dopamine receptors are densely expressed in striatal medium spiny neurons, but very few, co-express D1 and D2 receptors (Valjent et al., 2009); although they may express other dopamine receptor subtypes. Striatal D1- and D2-expressing medium spiny neurons are anatomically distinct, as they have non-overlapping projection targets (though this distinction may be less clear in the ventral striatum, see Kupchik et al., 2015), and activation of these two populations produces appetitive and aversive behavioral responses, respectively (Kravitz et al., 2012). While dopamine action in the striatum is by no means simple, the relatively clear-cut mRNA expression patterns of dopamine receptors in populations with diametrically opposed functions lend itself well to parsing the physiological and behavioral actions of dopamine in this area.

Indeed, controversy has long surrounded the topic of how dopamine alters the firing of mPFC neurons, and which types of neurons are affected. Seemingly contradictory results from different groups performing whole-cell patch-clamp recordings from pyramidal neurons in Layer 5 of mPFC have reported dopamine-induced increases (Penit-Soria et al., 1987; Yang and Seamans, 1996) or decreases (Bunney and Aghajanian, 1976; Gullledge and Jaffe, 1998) in activity. One possible explanation is that because the neurons were randomly sampled from Layer 5, different studies may have recorded from different projection and/or genetic subpopulations due to sampling bias. This notion is supported by more recent studies demonstrating that different cell types in mPFC display differential responses to dopamine (Gee et al., 2012; Tritsch and Sabatini, 2012, Vander Weele et al., 2018)

In the mPFC, dopaminergic terminals synapse on both pyramidal neurons (Goldman-Rakic et al., 1989; Séguéla et al., 1988; Zhang et al., 2010) and GABAergic interneurons (Verney et al., 1990). Canonically dopamine exerts its postsynaptic effects on neuronal activity via two main types of receptors— D1-type (including D1 and D5) and D2-type (including D2, D3, and D4) (Gaspar et al., 1995; Santana et al., 2009; Seamans and Yang, 2004; Sesack and Bunney, 1989). Both D1 and D2 sub-types are G-protein-coupled receptors, exerting slow, metabotropic modulation of postsynaptic cells (for review, see: Seamans and Yang et al., 2004). Activation of D1 receptors in the mPFC produces excitatory effects through modulation of sodium (Na⁺), potassium (K⁺), and calcium (Ca²⁺) currents (González-Burgos et al., 2002; Gorelova and Yang, 2000; Henze et al., 2000; Yang and Seamans, 1996). In contrast, activation of mPFC D2 receptors exerts an inhibitory effect through the modulation of glutamatergic receptors and Na⁺ conductances (Gorelova and Yang, 2000; Gullledge and Jaffe, 1998, 2001). However, receptor signaling and effects are complex in the mPFC (For extensive review, Seamans & Yang, 2004). For example, in both cases, activation of receptors can produce long-lasting (~30 min) or biphasic changes in excitability (Gorelova and Yang, 2000; Gullledge and Jaffe, 1998, 2001; Seamans et al., 2001a, 2001b; Semans and Yang, 2004). Recent studies have demonstrated that D2 receptor signaling in the mPFC is often excitatory (Robinson and Sohal, 2017; Urs et al., 2016, 2017), which may also be developmentally dependent (Tseng and O'Donnell, 2007). Further, dopamine can also have domain-specific physiological effects. Dopamine gates neuronal excitability at the axon initial segment (Clarkson et al., 2017) which may be a mechanism to control action

potential initiation (Bender et al., 2010; Kole and Stuart, 2012). In this manner, dopamine may enhance signal-to-noise ratio within mPFC neurons and modulate their responses to presynaptic input. Finer investigations of dopamine's actions in the mPFC is warranted, particularly *in vivo* where inputs and endogenous circuitry are intact.

In the mouse mPFC, D1 and D2 receptors are expressed in both pyramidal neurons and GABAergic interneurons (Gaspar et al., 1995; Vincent et al., 1993). D1 receptors are primarily located on the dendritic spines and shafts of pyramidal neurons and on the axon terminals of putative GABAergic interneurons (Bergson et al., 1995a, 1995b; Muly et al., 1998). Further, D1 immunoreactivity is present on presynaptic axon terminals that form asymmetric (i.e., putative glutamatergic) synapses with mPFC dendrites (Paspalas and Goldman-Rakic, 2005), suggesting that dopamine may influence the excitability of mPFC neurons both directly, and indirectly through modulation of excitatory inputs. In pyramidal neurons, D1 and D2 receptors are expressed in Layer 5 (Gaspar et al., 1995; Gee et al., 2012; Santana et al., 2009; Seong and Carter, 2012) – one of the major output layers of the mPFC. D1 receptor mRNA is expressed in 20% Layer 5 neurons, whereas 25% express D2 (Santana et al., 2009). Using pharmacological approaches, dopamine has been shown to increase (Henze et al., 2000; Penit-Soria et al., 1987; Yang and Seamans, 1996) and decrease (Bunney and Aghajanian, 1976; Gullledge and Jaffe, 1998; Sesack and Bunney, 1989) the excitability mPFC neurons – suggesting differential modulation by dopamine depending on mPFC cell-type or projection target. However, the relatively low expression level of dopamine receptors in mPFC projection neurons suggest that a larger portion of Layer 5 pyramidal neurons are not directly modulated by dopamine, but may be subject to dopaminergic modulation of presynaptic inputs (Seamans et al., 2001b; Tritsch and Sabatini, 2012).

The mPFC also expresses D3-, D4-, and D5-receptors. In mPFC pyramidal neurons, the cellular distribution of D1- and D5-receptors overlap with each other, but have distinct ultra-structural targeting: D1-receptor immunoreactivity is enriched on dendritic spines, whereas D5-receptor immunoreactivity is more prominent on dendritic shafts (Bergson et al., 1995c). Bilateral activation of D1- and D5-receptors in the mPFC (via pharmacological SKF-38393 infusion) promotes the incubation of aversive memories (Castillo Díaz et al., 2017) suggesting that this population is involved in the regulation of emotional behaviors. While it has been suggested that D3- and D4-receptors are largely located on GABAergic interneurons (Khan et al., 1998), D3-expressing mPFC projection neurons have been identified (Clarkson et al., 2017). Pharmacological investigations implicate D4-receptors in the encoding of fear (Laviolette et al., 2005), but not reward-related (Woolley et al., 2008) memories, but its still unknown whether D4-receptors are expressed on any specific mPFC projection pathway. Considering there is emerging evidence that suggests that dopamine may differentially modulate specific mPFC projection pathways to optimize circuit computations that result in adaptive behavioral outcomes (Vander Weele et al., 2018), systematic investigation of anatomically distinct mPFC subpopulation could be the catalyst for a new age in understanding mesocortical dopamine (Figure 3).

Dopamine on mPFC-NAc

The heterogeneous effects of dopamine on the activity of post-synaptic cells in the mPFC, discussed above, has led to investigations into how dopamine may be differentially affecting projection-defined mPFC neurons. For example, VTA dopamine terminals have been shown to target mPFC neurons that project to the NAc (Carr et al., 1999). Not surprisingly, NAc-projecting mPFC neurons express D1 (Gaspar et al., 1995; Han et al., 2017, Vander Weele et al., 2018), D2 (Gaspar et al., 1995, Vander Weele et al., 2018), and D3 receptors (Clarkson et al., 2017), and their activity is modulated by dopamine (Brady and O'Donnell, 2004; Buchta et al., 2017, Vander Weele et al., 2018). Initial inquiry into the exact distribution and proportion of dopamine receptor expression in striatum-projecting neurons found that ~20% express D1 and 60% express D2 – however this investigation did not isolate neurons projecting to the NAc from neurons projecting to other striatal regions (e.g., dorsal striatum) (Gaspar et al., 1995). Recently, we employed transgenic D1- and D2-Cre mouse driver lines and retrograde labeling to specifically examine dopamine receptor expression on NAc-projecting mPFC neurons, and found slightly higher D1 (~30%) and D2 (~85%) receptor expression (Vander Weele et al., 2018). These difference could be due to the developmental caveats of using transgenic reporter lines (Chan et al., 2012; Tritsch and Sabatini, 2012) or the differentiation of the NAc from other striatal regions. Despite these differences, based on the predominance of D2 expression in both studies, we predicted that the mPFC-NAc circuit would be inhibited by dopamine. Indeed, we found that Layer 5 neurons projecting to the NAc were inhibited by activation of VTA dopamine terminal in *ex vivo* brain slices, an effect that was dependent on D2-receptors (Vander Weele et al., 2018). These data are consistent with *in vivo* interrogations of this pathway, which report similar inhibitory actions by dopamine via D2 receptors (Brady and O'Donnell, 2004). Together, it appears that dopamine largely inhibits the mPFC to NAc pathway (but see: Buchta et al., 2017). Given the role of mPFC projections to the NAc in promoting reward-seeking, discussed above, we hypothesize that dopamine-induced inhibition of this circuit acts as a permissive signal for aversive information to be routed downstream through complimentary circuits.

Dopamine on mPFC-PAG

In contrast to the role of mPFC neurons projecting to the NAc in reward seeking, projections to the PAG regulate aversive behavioral responses; however, this pathway does not appear to robustly express dopamine receptors. Indeed, only sparse labeling of terminals is observed in the PAG of D1 transgenic mice (Han et al., 2017). Further, we have investigated this question using D1- and D2-Cre driver lines combined with retrograde labeling and found that only ~5% of mPFC-dPAG projectors express D1 receptors, and ~20% express D2 receptors (Vander Weele et al., 2018). This was corroborated by functional studies showing that VTA dopamine terminal stimulation does not affect excitability of this circuit in *ex vivo* brain slices (Vander Weele et al., 2018). However, evidence supports indirect modulation of mPFC pyramidal neurons by dopamine — either via interactions with local GABAergic interneurons or modulation of other inputs (Paspalas and Goldman-Rakic, 2005; Seamans et al., 2001b; Tritsch and Sabatini, 2012), which motivated us to test the impact of dopamine on this projection *in vivo* where the circuitry required for indirect modulatory mechanisms is still intact. In *in vivo* preparations we have found that dopamine increases signal-to-noise ratio in mPFC-dPAG neurons during processing of aversive stimuli (Vander Weele et al.,

2018). Specifically, VTA dopamine terminal stimulation enhanced neural responses to airpuff in photoidentified mPFC-dPAG neurons, but did not effect responses to sucrose delivery. In the homecage where no aversive stimuli were present, single-cell calcium imaging recordings revealed that VTA dopamine terminal stimulation enhanced the amplitude of individual calcium transients in mPFC-dPAG neurons but decreased there overall frequency – perhaps by filtering relevant inputs or changing the pattern of firing. Indeed, we found that VTA dopamine terminal stimulation selectively increased the average frequency within a burst firing event within mPFC-dPAG (Vander Weele et al., 2018), effectively increasing the signal-to-noise ratio between burst and baseline firing. Considering calcium transient amplitude linearly related to the number of spikes within a burst event (Chen et al., 2013; Otis et al., 2017), this pattern of firing may underlie changes in calcium event amplitude. These data suggest that dopamine in the mPFC may promote the encoding and subsequent behavioral responses to aversive stimuli by modulating incoming inputs impinging upon the mPFC-dPAG circuit.

Dopamine on mPFC-BLA

Several studies suggest that mPFC-BLA neurons express D1 (Han et al., 2017; Land et al., 2014; Rey et al., 2014) and perhaps to a lesser degree D2 (Pinto and Sesack, 2008; Rosenkranz and Grace, 2001), and D3 (Clarkson et al., 2017) – although the exact proportions are still unclear. Unlike projections to the NAc and dPAG (Vander Weele et al., 2018), anatomical investigations using retrograde tracing and dopamine receptor labeling in the mPFC-BLA have yet to be completed. Although the mPFC-BLA connection has largely been studied in the context for fear and aversive responses, specific activation of mPFC D1-expressing terminals in the BLA promotes feeding (Land et al., 2014), a behavior typically regarded as reward-related. However, functional heterogeneity also exists within the BLA (Beyeler et al., 2016; Kim et al., 2016b; Namburi et al., 2015). Given that D1 and D2 receptor activation differentially influence BLA neuronal responses to mPFC input (Rosenkranz and Grace, 2002), it is tempting to speculate that via this mechanism dopamine could route information about positive and negative stimuli to specific subpopulations of neurons responsible for valence-encoding within the BLA. Future studies dissecting the precise connectivity and behavioral operations of mPFC D1- and D2-expressing inputs to the BLA could yield exciting new insights. To date, there is not enough evidence to form conclusions regarding how dopamine directs the flow of information about motivationally-relevant stimuli within the mPFC-BLA circuit.

Dopamine on mPFC-thalamus and other circuits

Even less is known about dopaminergic modulation of other mPFC projections, including those to the MD and PVT. Although we've known that ~25% of mPFC-MD neurons express D1 mRNA for some time (Gaspar et al., 1995; Han et al., 2017), little is known about their cognitive or behavioral functions. Interestingly, while most mPFC-MD projectors reside in Layer 6 and do not express D2 receptor (Gaspar et al., 1995), a small population of MD projectors reside in Layer 5 and almost exclusively express D2 (Gee et al., 2012). Given this stark contrast, interesting functional differences between Layer 5 and Layer 6 mPFC-MD pathways may be revealed in the future. Dopamine receptor localization on other projectors, including the PVT is still unclear; however, a recent anatomical characterization D1

transgenic driver line suggest that mPFC D1 neurons may also project to the dorsal striatum, claustrum, and ventral thalamus (Han et al., 2017). D3-expressing mPFC neurons have been identified within mPFC-NAc, mPFC-BLA, and mPFC-MD projection pathways (Clarkson et al., 2017), as discussed in the sections above. However, the precise behavioral function of these specific subpopulations has yet to be determined.

8. Dopamine in the mPFC sets the tone for aversive circuit computations

In summary, midbrain dopamine neurons are critically involved in modulating neural circuits responsible for appetitive and aversive motivation. While the impact of dopamine release within the striatum is studied extensively, particularly in the context of reward-related behaviors, the mesocortical pathway's role in motivation has been relatively understudied. Mounting evidence suggests that under certain conditions, the responsiveness of the mesocortical system to aversive stimuli may promote behavioral coping strategies in response to aversive outcomes and threatening stimuli (Lammel et al., 2011, 2012; Vander Weele et al., 2018). Further, considering mPFC neurons are responsive to both rewarding and aversive stimuli (Burgos-Robles et al., 2009, 2013; Euston et al., 2012), it is possible that mPFC neuronal circuits encoding aversive or rewarding events are differentially modulated by dopamine – a theory supported by emerging results (Vander Weele et al., 2018) (Figure 4). This flexibility in function can result in a vast array of computations and behavioral outcomes that could highly depend on environmental context. For example, in environments where only reward-related stimuli are present, perhaps dopamine in the mPFC functions to optimize reward-learning and acquisition. However, when threatening stimuli are present, an organism must rapidly and efficiently respond to avoid harm. Perhaps in these situations, the sensitivity of mesocortical dopamine to aversive stimuli serves as a robust strategy-switching signal to aid in threat avoidance. In these situations, dopamine would set the stage for aversive processing by amplifying inputs onto cortical pathways essential for escape and avoidance, while suppressing information that does not require immediate action.

The notion that dopamine can alter signal-to-noise is attractive, as dopamine-mediated increases in signal-to-noise ratio could explain its diverse behavioral and cognitive functions. Despite the popularity of the signal-to-noise model for mPFC dopamine in computational and theoretical neuroscience (Cohen and Servan-Schreiber, 1992; Cohen et al., 2002; Durstewitz and Seamans, 2008; Rolls et al., 2008), the degree to which it translates across brain functions is unknown. Support for dopamine-mediated signal-to-noise ratio modulations has been found *ex vivo* (Kroener et al., 2009; Seamans et al., 2001b), and *in vivo* during auditory stimulus discrimination (Popescu et al., 2016), working memory (Williams and Goldman-Rakic, 1995), and visual cortex orientation selectivity (Noudoost and Moore, 2011). Dopamine may function similarly within the mPFC to optimize motivated behaviors. Our recent findings show that dopamine release serves to sharpen responses to motivationally significant stimuli by simultaneously enhancing the signal-to-noise in aversion-encoding pathways and inhibiting pathways that contribute to other behaviors. Therefore, while it is still debated whether mesocortical dopamine release is innately aversive (Ellwood et al., 2017; Gunaydin et al., 2014; Popescu et al., 2016; Vander Weele et al., 2018), we propose that mesocortical dopamine promotes responding to aversive

stimuli when necessary via the fine-tuning of cortical subpopulations carrying information of positive or negative valence.

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HIGHLIGHTS

- Dopamine has diverse actions on prefrontal cortex physiology and function.
- The mesocortical dopamine pathway is uniquely sensitive to aversive stimuli.
- Dopamine differentially influences projection-defined prefrontal subpopulations.
- By calibrating distinct prefrontal outputs, dopamine sets the stage for aversive processing.

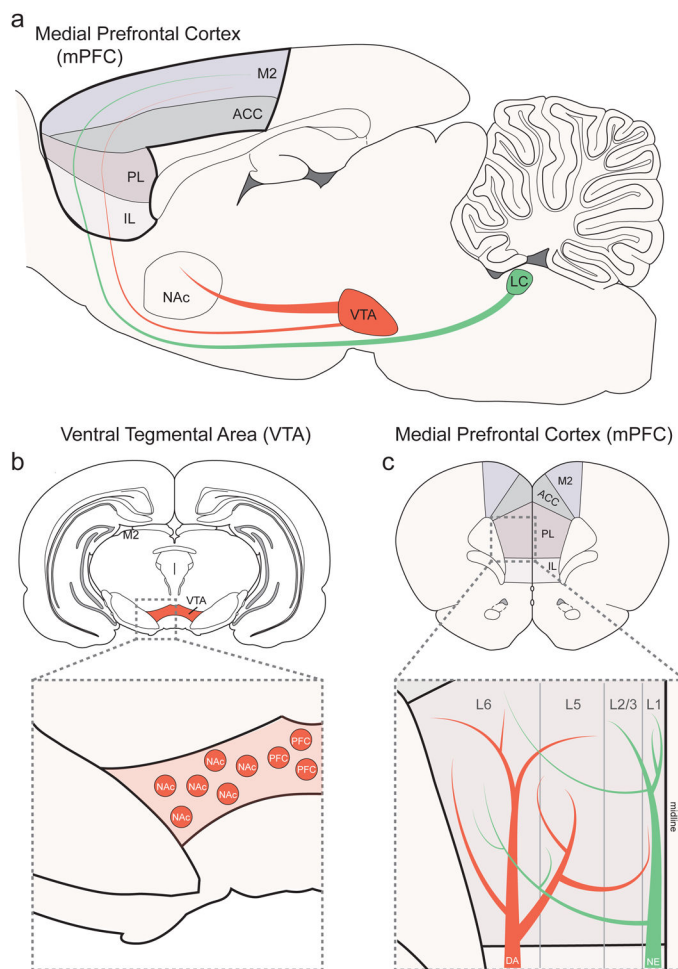


Figure 1.

Catecholaminergic innervation of the corticolimbic system. **a.** Sagittal section of the rat brain showing catecholaminergic innervation of the medial prefrontal cortex (mPFC) and its four major subdivisions: secondary motor cortex (M2), anterior cingulate cortex (ACC), prelimbic cortex (PL), and infralimbic cortex (IL). Dopamine neurons originate from the ventral tegmental area (VTA) and project to the mPFC and ventral striatum / nucleus accumbens (NAc). Norepinephrine neurons in the locus coeruleus (LC) travel below the VTA to the mPFC and other corticolimbic regions. **b.** Coronal section of the rat brain showing the location of the VTA on an anterior-posterior axis. Inset shows the medial-lateral distribution of projection defined VTA dopamine neurons. Mesocortical dopamine neurons reside in the more medial aspects of the VTA and mesolimbic dopamine neurons reside in the more lateral aspects. **c.** Coronal section of the rat brain showing the mPFC and its major subregions on an anterior-posterior axis. Inset shows catecholaminergic innervation of mPFC layers. Dopaminergic axon terminals preferentially innervate the deep layers of the mPFC (Layers 5–6), while noreadrenergic axon terminals preferentially innervate the superficial layers (Layers 1–2/3). Abbreviations: DA = dopamine; NE = norepinephrine.

	Mesolimbic Dopamine Pathway (VTA-NAc)	Mesocortical Dopamine Pathway (VTA-PFC)
Density of Projection	robust	sparse
Soma Location in VTA	lateral	medial
Ih Current	yes	no
Waveform	conventional	unconventional
Firing Rate	low baseline, low bursting	high baseline, high bursting
Reuptake / Degradation	fast	slow
Presence of Autoreceptors	yes	no
Response to Reward	+++	+ or x
Response to Punishment	+ or -	+++
Major Input(s)	laterodorsal tegmentum	lateral habenula rostromedial tegmentum

Figure 2.
Abridged summary of differences between the mesolimbic and mesocortical dopamine pathways.

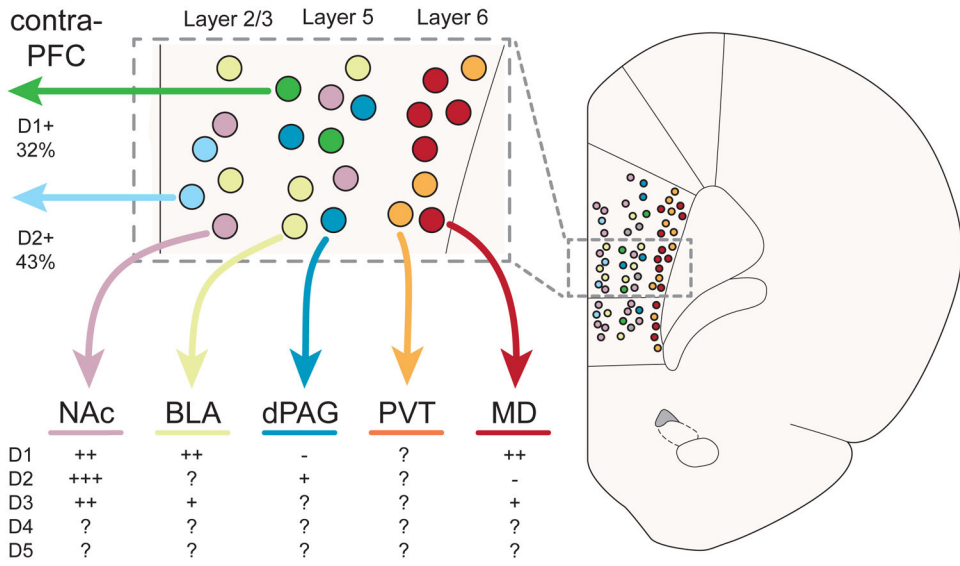


Figure 3. Laminar origins of select mPFC projection populations and their dopamine receptor expression. Abbreviations: BLA = basolateral amygdala; contra-PFC = contralateral prefrontal cortex; dPAG = dorsal periaqueductal gray; MD = mediodorsal thalamus; NAc = nucleus accumbens; PVT = periventricular nucleus of the thalamus.

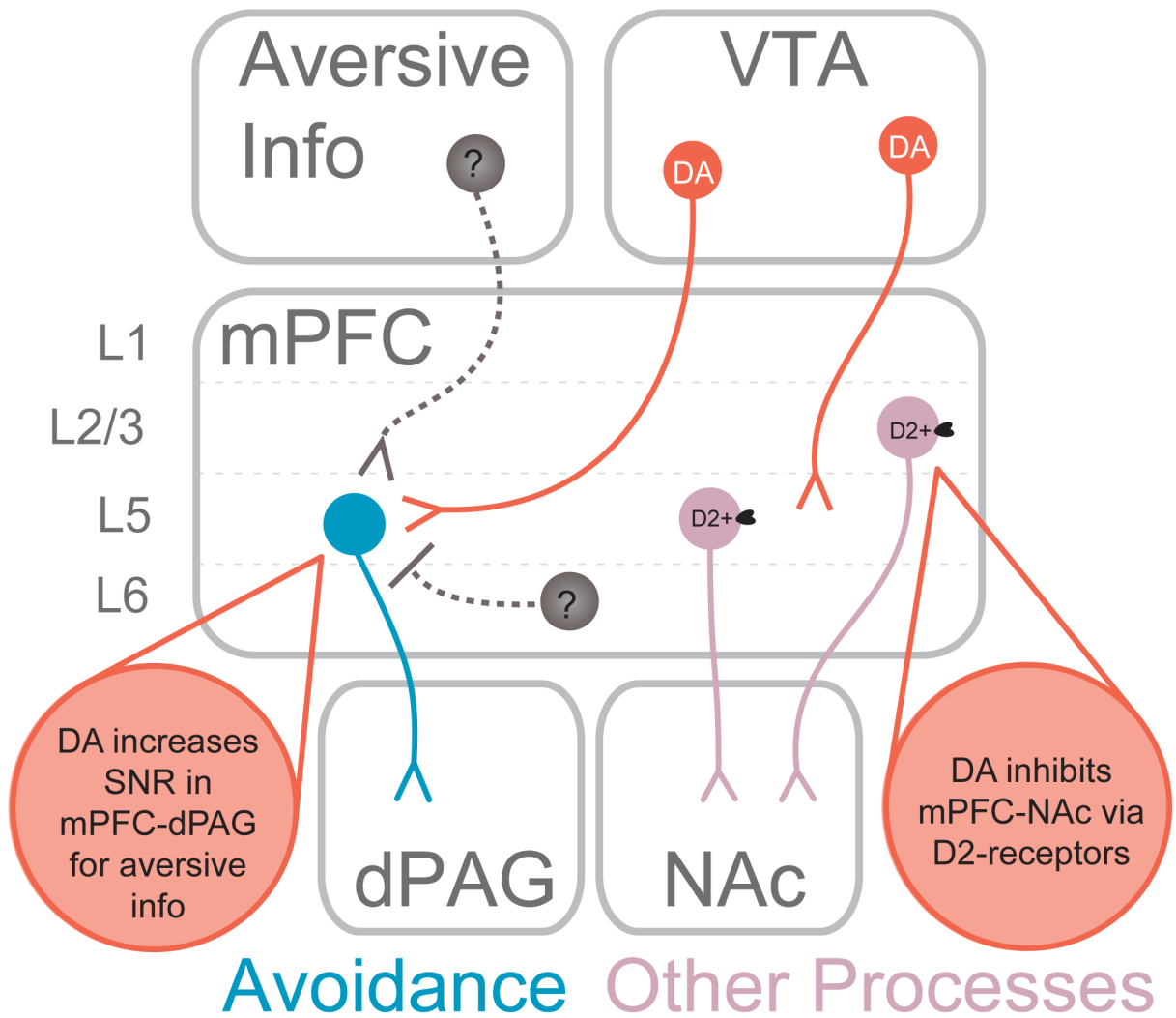


Figure 4. Summary of findings found in Vander Weele et al., 2018. Threatening events evoke dopamine release in the mPFC which enhances the signal-to-noise ratio of responses to aversive stimuli within the mPFC-dPAG pathway. Dopamine suppresses excitability of neurons in the mPFC-NAc pathway via D2-receptors. These actions support adaptive behavioral responses to threat, such as avoidance.