CHAPTER SEVEN

Valence processing in the PFC: Reconciling circuit-level and systems-level views

Austin A. Coley[†], Nancy Padilla-Coreano[†], Reesha Patel[†], and Kay M. Tye*

Salk Institute for Biological Studies, La Jolla, CA, United States
*Corresponding author: e-mail address: tye@salk.edu

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[†] These authors contributed equally.

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Abstract

An essential component in animal behavior is the ability to process emotion and dissociate among positive and negative valence in response to a rewarding or aversive stimulus. The medial prefrontal cortex (mPFC)—responsible for higher order executive functions that include cognition, learning, and working memory; and is also involved in sociability—plays a major role in emotional processing and control. Although the amygdala is widely regarded as the "emotional hub," the mPFC encodes for context-specific salience and elicits top-down control over limbic circuitry. The mPFC can then conduct behavioral responses, via cortico-striatal and cortico-brainstem pathways, that correspond to emotional stimuli. Evidence shows that abnormalities within the mPFC lead to sociability deficits, working memory impairments, and drug-seeking behavior that include addiction and compulsive disorders; as well as conditions such as anhedonia. Recent studies investigate the effects of aberrant salience processing on cortical circuitry and neuronal populations associated with these behaviors. In this chapter, we discuss mPFC valence processing, neuroanatomical connections, and physiological substrates involved in mPFC-associated behavior. We review neurocomputational and theoretical models such as "mixed selectivity," that describe cognitive control, attentiveness, and motivational drives. Using this knowledge, we describe the effects of valence imbalances and its influence on mPFC neural pathways that contribute to deficits in social cognition, while understanding the effects in addiction/compulsive behaviors and anhedonia.

1. Introduction

The medial prefrontal cortex (mPFC), a prominent brain region located within the frontal lobe, is primarily responsible for functions that include decision-making processes and judgement (Bechara, Damasio, & Damasio, 2000); attentional processing (Miller & Buschman, 2013), learning and memory consolidation (Euston, Gruber, & McNaughton, 2012); as well as working memory (Goldman-Rakic, 1996; Sawaguchi & Goldman-Rakic, 1991), social cognition (Forbes & Grafman, 2010) and emotional processing (Etkin, Egner, & Kalisch, 2011). However, this chapter will highlight the critical role of mPFC circuits and neuronal ensembles in emotional processing in the context of mood disorders, drug addiction and social cognition due to their direct relevance to emotional regulation, and provide a more harmonious and

unified view of mPFC function incorporating both circuit-level and systems-level insights and conceptual frameworks.

An important feature in emotional processing is the ability to integrate sensory information—via external inputs and homeostatic internal states—to trigger a specific emotional and behavioral response. In animals, emotions can impact survival, reproduction, motivation, and decision-making processes.

From a basic science perspective, the urgency is necessitated by the rapid proliferation of literature in two diametrically-opposed conceptual frameworks underpinning PFC function. We have witnessed the paradigm-shifting emergence of a systems-level conceptual framework highlighting (nonlinear) "mixed selectivity" of PFC neurons, which not only suggests that individual neurons may be selectively responsive to many parameters under different contexts and are thereby recruited to multiple, seemingly-distinct functions in different contexts, but also provides a systems-level explanation for how the mPFC is endowed with high functioning processing power (Allsop, Vander Weele, Wichmann, & Tye, 2014; Johnston, Palmer, & Freedman, 2020; Muir, Lopez, & Bagot, 2019; Riga et al., 2014; Vander Weele et al., 2018; Vander Weele, Siciliano, & Tye, 2018). The concept of flexibility in function is juxtaposed with accumulating evidence—and canonical circuit diagrams—depicting PFC circuits as for diverse, but implicitly fixed, functions ascribed to specific components by the input-output ("hardwired") architecture of the circuit. (Allsop et al., 2014; Muir et al., 2019; Riga et al., 2014; Siciliano et al., 2019; Vander Weele et al., 2018; Vander Weele, Siciliano, & Tye, 2018).

The often-overlooked function of mPFC valence processing is essential in distinguishing among motivational drives of reward and aversion. In the two-dimensional model of valence and arousal (Lang, 1995), valence is assigned as a positive (pleasant) or negative (unpleasant) hedonic value, whereas arousal illustrates the intensity or degree of the emotional state (Lang, Bradley, & Cuthbert, 1990; Russell, 1980; Tye, 2018). Indeed, the mPFC provides context-dependent valence processing that influences behaviors.

The mPFC elicits top-down control over subcortical regions such as the basal ganglia and limbic structures that affect memory, motivation, and emotional behaviors (Miller & Cohen, 2001). Consequently, mPFC dysfunction alters behavioral output. For instance, lesions to the mPFC and orbital frontal cortex (OFC) reveal a loss of emotional inhibitory control, impaired attentional processing (Dias, Robbins, & Roberts, 1996), reactive aggression (Anderson et al., 2007; Grafman et al., 1996; Pennington & Bennetto,

1993), and a reduction in social cognition (Blair & Cipolotti, 2000; Hornak, Rolls, & Wade, 1996). Other studies showed the mPFC is implicated in context-dependent drug-reward seeking behavior and compulsive disorders (Bossert et al., 2011, 2012), and displays disrupted processing during anhedonia due to dopamine (DA) imbalances (Callicott et al., 2003; Ferenczi et al., 2016; Hamani et al., 2011).

In an effort to better understand how seemingly static circuits mediate these dynamic behaviors, we review neurocomputational models of mixed selectivity, that describe complex and prominent features of the mPFC, and integrate circuit-level function into a conceptual framework in which to understand valence processing mPFC circuits across a wide-range of behaviors.

We highlight the role of the mPFC in emotional valence processing with a focus on mPFC neural circuits mediating reward and social behaviors. Although the mPFC is involved in myriad of emotional behaviors that include fear expression/extinction and response to threat (Sotres-Bayon & Quirk, 2010), we focus on the mPFC circuits encoding valence and its role in social behaviors, and how valence processing is disrupted during addiction and anhedonia.

2. The mPFC encodes context-specific valence processing

2.1 Emotional processing in the mPFC vs the amygdala

While the limbic system has been largely conserved across evolution (Janak & Tye, 2015), the PFC represents the most dramatic and significant evolutionary changes in the brain (Fig. 1). Among these species, the PFC is considerably larger in primates, and largest in absolute size within humans (Brodmann, 1909; Semendeferi, Damasio, Frank, & Van Hoesen, 1997; Semendeferi, Lu, Schenker, & Damasio, 2002), suggesting a major role for higher-order functional processing in this region. The human prefrontal cortex (PFC) can be divided into dorsolateral (dlPFC), ventrolateral (vlPFC), dorsomedial (dmPFC), ventromedial (vmPFC) and orbitofrontal (OFC) regions (Passingham & Wise, 2014); although neuroanatomists argue the topographic maps of subdivisions within the PFC (Carmichael & Price, 1994; Ongür, Ferry, & Price, 2003; Petrides, 1995). The mPFC in rodents, including mouse and rats, can be subdivided into three primary regions: the anterior cingulate cortex (ACC), the prelimbic cortex (PL) and infralimbic cortex (IL) (Heidbreder & Groenewegen, 2003; Ongür & Price, 2000).

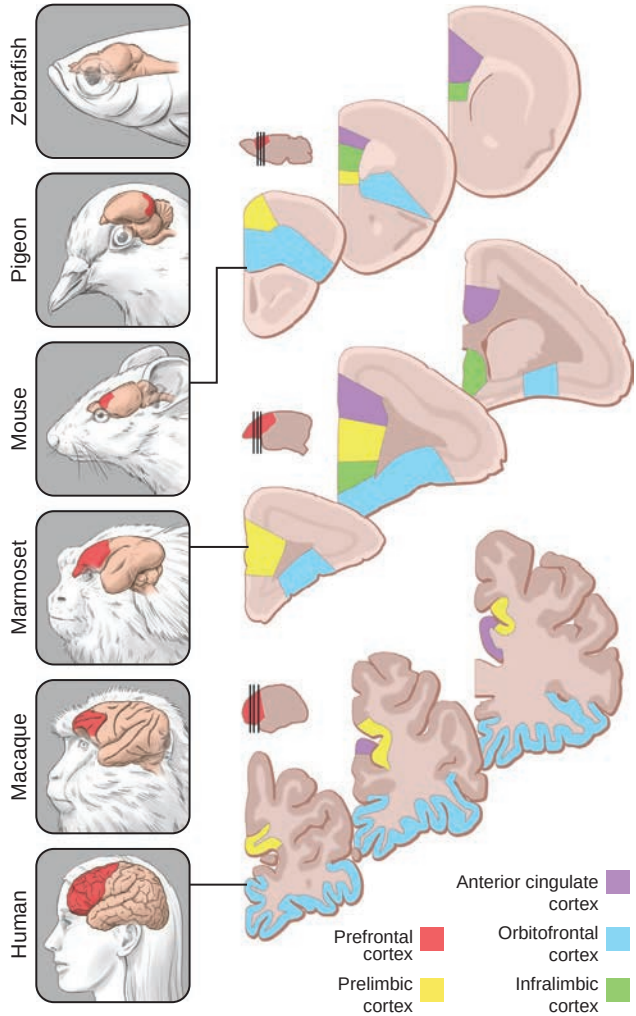

Fig. 1 Evolutionary changes of the PFC across species. The relative size and location of the prefrontal cortex (PFC; red) significantly differs among species: zebrafish (none), pigeon, mouse, marmoset, macaque, and human. Analogous PFC subregions are represented in coronal sections in the mouse, marmoset and human. Prelimbic cortex (yellow), anterior cingulate cortex (purple), orbitofrontal cortex (blue), and infralimbic (green).

However, some studies include the secondary motor cortex (M2) in the mPFC (Donoghue & Wise, 1982; Gabbott, Warner, Jays, Salway, & Busby, 2005), which remains debatable (Laubach, Amarante, Swanson, & White, 2018).

The mPFC plays an essential role in regulating emotions and salience processing by integrating multimodal sensory inputs and facilitating behavioral outputs dependent on context (Miller, 1999; Miller & Cohen, 2001; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). In this respect, the mPFC elicits top-down control of limbic and brainstem regions that influence emotional behavior (Grace, Floresco, Goto, & Lodge, 2007; Lee & D'Esposito, 2012; Ochsner et al., 2009; Ochsner, Bunge, Gross, & Gabrieli, 2002; Quirk & Beer, 2006). Indeed, there are multiple circuit nodes that have been implicated in emotional processing, including the amygdala (Allsop et al., 2018; Burgos-Robles et al., 2017; Yizhar & Klavir, 2018), ventral hippocampus (vHP) (Fanselow & Dong, 2010), and ventromedial hypothalamus (VMH) (Kunwar et al., 2015); whereas the amygdala and a subdivision of the VMH has direct reciprocal connections with the mPFC (Lo et al., 2019; Yizhar & Klavir, 2018).

In contrast to the mPFC, the amygdala—widely considered the hub for emotional processing (Brown & Sharpey-Schafer III, 1888; Janak & Tye, 2015; Klüver & Bucy, 1937; LeDoux, 1996; Maren & Quirk, 2004; Tye, 2018; Weiskrantz, 1956)—provides bottom-up control in limbic circuitry, thereby facilitating rapid (LeDoux, 1996; Méndez-Bértolo et al., 2016; Tamietto & de Gelder, 2010), and automatic processing of emotions in response to salient stimuli, in addition to modulating attention and motivated-behavior (Davis & Whalen, 2001; LeDoux, 2000; Ochsner et al., 2009; Phelps & LeDoux, 2005). The amygdala is also involved in regulating fear responses (Fanselow & LeDoux, 1999; Maren, 2001). For instance, in the historical case study that examined patient S.M., diagnosed with Urbach-Wiethe disease, Adolph et al showed bilateral damage of the amygdala severely impairs fear and anger recognition in facial expressions. However, patient S.M. revealed no deficits in facial identity recognition, indicating the amygdala's role in facial affects and discerning emotional associations (Adolphs, Tranel, Damasio, & Damasio, 1994).

Indeed, the basolateral amygdala complex (BLA), that includes the lateral, basolateral, and basal amygdala nuclei, identified as an essential area in fear conditioning consists of specific neuronal populations involved in the acquisition of associative memories as well as retrieval (Clem & Huganir, 2010; Fanselow & Dong, 2010; Han et al., 2007, 2009; Namburi et al., 2015; Reijmers, Perkins, Matsuo, & Mayford, 2007; Rumpel, LeDoux, Zador, & Malinow, 2005). Whereas within the PFC, the acquisition, encoding and retrieval systems appear to be in distributed neuronal populations (Otis et al., 2017; Siciliano et al., 2019; Vander Weele et al., 2018). Although, within other

emotional nodes such as the ventromedial hypothalamus, require specific neuronal populations activation that differentiate aggression and mating behaviors (Lin et al., 2011). These studies highlight key distinctions in neuronal circuits as well as cell properties among limbic regions and the PFC in emotional behavior.

2.2 The mPFC and emotional control

Another facet of mPFC valence processing is its involvement in emotional control and the ability to suppress impulse behavior. Previous studies in non-human primates showed damage to the OFC and lateral PFC elicits deficits in affective processing as well as attentional selection (Brozoski, Brown, Rosvold, & Goldman, 1979; Dias et al., 1996). Specifically, the mPFC, along with other circuits, play a role in inhibiting rage and aggression (Aleyasin, Flanigan, & Russo, 2018). In perhaps the earliest study examining the effects of frontal lobe damage, patient Phineas Gage, suffered severe prefrontal cortex damage during a work accident. Following the incident, Gage experienced significant cognitive and emotional changes that included learning deficits as well as irritable, hostile, capricious, and irrational behavior (Harlow, 1868, 1993). Thus, the PFC was targeted as a region for experimentation to control anomalous behavior. Early procedures, i.e., the psychosurgical interventions of the prefrontal leucotomy, now described as the "lobotomy," was developed to control human emotional and psychotic behavior in mental health patients (Moniz, 1937). The technique was designed to reduce aggressive tendencies by removing white matter that undercut afferent and efferent connections to the PFC. Although highly controversial and inconsistent, the PFC was highlighted as a region implicated in emotional inhibition (Abimbola & Awolowo, 2006; Tierney & Egas, 2000).

Historical evidence derived from human lesion studies corroborate the effects of aberrant emotional behavior sustained by prefrontal cortex damage (Papez, 1937). For example, human studies showed that patients exhibiting ventrolateral and OFC damage display increased risk-taking and maladaptive behaviors related to reward-based aspects in decision-making processes (Floden, Alexander, Kubu, Katz, & Stuss, 2008). Specifically, lesions within the OFC (which often includes the ventromedial PFC; vmPFC), a region involved in assessing reward-outcome and value (Wallis & Orbitofrontal, 2007), lead to increased risk-behavior regardless of the outcome or consequence (Bechara, Damasio, Damasio, & Anderson, 1994; Clark et al., 2008).

It was also shown that vmPFC lesions lead to emotional deficits that included irritability, anxiety, as well as social impairments (Anderson, Barrash, Bechara, & Tranel, 2006).

Bilateral lesions to the OFC lead to impairments in identifying voice and facial expressions, along with deficits in subjective emotional states and awareness (Hornak et al., 2003; Tsuchida & Fellows, 2012). Unilateral lesions to the anterior cingulate cortex showed similar deficits in voice and facial expressions identification and changes in subjective emotional states (Hornak et al., 2003). A subtle distinction in these studies compared to the bilateral amygdala lesions, as observed in patient S.M., is the specific absence of fear and anger in facial recognition (Adolphs et al., 1994; Forbes & Grafman, 2010; Fusi, Miller, & Rigotti, 2016; Rigotti et al., 2013) .These human lesion studies highlight the effects of PFC damage as it relates to emotional control, as well as the assessment of affective states in reward processing and motivation.

2.3 The mPFC and context-specificity

The mPFC is principally involved in executive functions, that includes cognitive processing and working memory, and is highly influenced depending on contextual information (Bechara et al., 2000; Euston et al., 2012; Sawaguchi & Goldman-Rakic, 1991). Context can be defined as a situation or circumstance describing an event and can be delineated into multiple aspects that include spatial, temporal, physiological, social, and/or cognitive contexts (Maren, 2001). Context can provide information regarding location and objects surrounding an environment, or actions and thoughts of an event occurring during time. Context can also be described as the internal or physiological state, for example hunger or stress; and depict the social environment that influences behavioral outcomes. Furthermore, a cognitive context is critical for encoding or processing information, and the retrieval of memories which is necessary for adaptive behavior. As a higher-order cortical region, the mPFC utilizes context during emotional valence processing that affect goal-directed behaviors and decision-making processes (Kennerley & Walton, 2011).

2.4 Mixed selectivity as a framework to flexibly encode valence in mPFC circuits

Neurons that respond to stimuli in a specific condition or context or that respond to a combination of task variables are referred to as 'mixed selectivity' cells (Fusi et al., 2016; Grunfeld & Likhtik, 2018; Parathasarathy et al., 2017;

Ramirez-Cardenas & Viswanathan, 2016; Rigotti et al., 2013). We propose that mixed selectivity is a model that can explain how mPFC circuits flexibly encode valence across contexts and situations. In the wild, animals encounter a range of contexts with varying degrees of risk and reward probabilities. Imagine the toy example of two contexts, one with high probability of reward and another with high probability of risk (Fig 2). mPFC neurons could respond to specific valence cues in a context-specific manner, thus encoding a combination of valence and risk level. Mixed selectivity is computationally advantageous because it increases the dimensionality of the population activity which allows for more efficient encoding of complex tasks, thus highlighting the ensemble of neurons, and not an individual cell, as the coding unit (Fusi et al., 2016; Johnston et al., 2020; Rigotti et al., 2013).

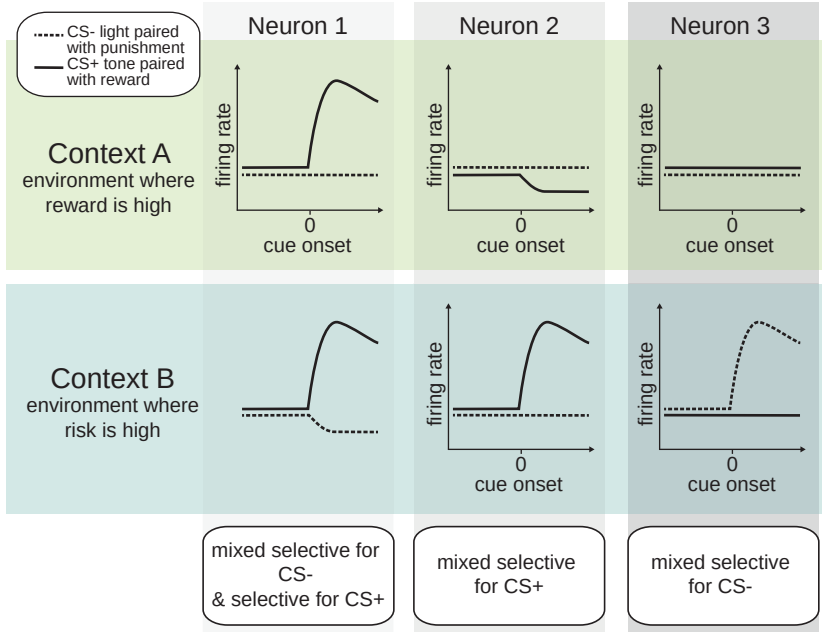

Fig. 2 Mixed selectivity in valence encoding cells. Toy example using cue and contexts as parameters and showing mixed selectivity for neurons that encode a positive CS+ cue that predicts a reward or a negative CS- cue that predicts a punishment. Top row shows firing rate to CS+ and CS- for 3 hypothetical neurons in context A which has high probability of reward. Middle row shows firing rate for the same 3 neurons in context B which has a high-risk probability. Bottom row indicates if neurons display nonlinear mixed selectivity. No individual neuron represents the 4 conditions, but the combination of the firing rate from the 3 neurons can be used to decode condition.

In both primates and rodents, the prefrontal cortex shows mixed selectivity during decision making and working memory assays (Machens, Romo, & Brody, 2010; Mante, Sussillo, Shenoy, & Newsome, 2013; Naya, Chen, Yang, & Suzuki, 2017; Powell & Redish, 2014). These types of PFC mixed selective cells are easiest to identify when using intricately-designed, model-driven behavioral experiments that are common in systems-level investigations of non-human primates. On the other hand, most circuit-specific studies use a data-driven approach, employing reductionist assays for their reproducibility and use manipulations complicating or even obscuring the identification of mixed selective cells. In addition, valence encoding literature has historically centered around single-cell (Kyriazi, Headley, & Pare, 2018; Paton, Belova, Morrison, & Salzman, 2006; Shabel & Janak, 2009) or populations of cells that are anatomically defined (Beyeler et al., 2016, 2018; Ciocchi et al., 2010; Janak & Tye, 2015; Namburi et al., 2015; Tye et al., 2011) encoding, thus overlooking what the population is encoding as a whole.

Rigotti and colleagues demonstrated that the encoding advantage of mixed selectivity is due to the nonlinear combination of firing rate to two parameters. We propose circuit motifs to provide a neurobiological mechanism for non-linear mixed selectivity and help consolidate this useful neural code scheme with the hardwiring of circuits. First, convergence of functionally diverse inputs of varying synaptic strength to the same mPFC neurons could lead to nonlinear encoding of multiple parameters underlying mixed selectivity (Fig. 3; motif 1). In addition, microcircuitry of mPFC cells with diverse functions and interneurons could lead to mixed selectivity (Fig. 3; motif 2). An example of this microcircuit motif was seen in the amygdala, as a recent study showed that two amygdala subpopulations that encode opposing valence are interconnected and modulated by hunger (Calhoon et al., 2018). Internal states, such as hunger, social rank and mood can modulate excitability or promote plasticity to non-linearly modulate firing rate, thus promoting non-linear mixed selectivity across states. These two motifs explain potential circuitry for a neuron to show mixed selectivity, however they do not explain how there can be flexible routing of behavioral output. We propose that a postsynaptic gating circuit motif can explain how mixed selectivity in neurons with collateral projections can allow flexible behavioral outputs. Postsynaptic gating via axo-axonal inhibition or context or state-induced changes in intrinsic excitability could gate the specific downstream pathway that is promoted (Fig. 3; motif 3). Finally, neuromodulators can help bias a given behavioral output. We propose a

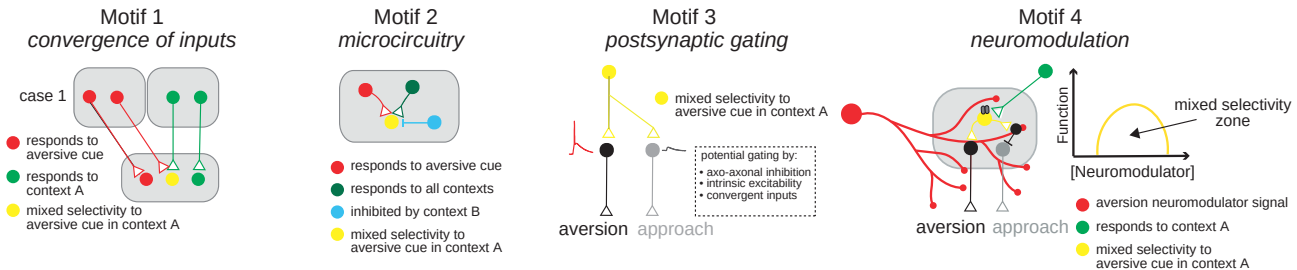

Fig. 3 Circuit motifs as neurobiological mechanisms for mixed selectivity. All motifs represent a mixed selective cell that fires to an aversive cue in a specific context A. Motif 1 shows that the same neuron receives converging input with different synaptic strengths from one input that responds to the aversive cue and another that responds to context A, leading to non-linear mixed selectivity. Motif 2 shows an example of mixed selectivity arising from local microcircuitry. Notice that the mixed selectivity is happening from context and cue information converging locally while inhibition facilitates context selectivity. Motifs 1 and 2 explain how non-linear mixed selectivity can arise from connectivity, while motifs 3 and 4 focus on how circuitry can enable flexible behavioral selection downstream. Motif 3 focuses on gating mechanisms in the downstream regions recruited by mixed selective mPFC cells with collateral projections. Gating mechanisms in the downstream cells, such as axo-axonal inhibition, intrinsic excitability, or converging inputs, can determine which pathway is promoted. Motif 4 -shows a neuron that receives input from a neuromodulator that responds to aversion signals and input that is modulated by context A, which together promote context-specific aversion. By recruiting inhibition of mPFC pathways that promote approach the mixed selective neuron can help route behavioral selection.

motif in which neuromodulator concentration promotes mixed selectivity in mPFC. A recent study showed that dopamine is released to the mPFC and promotes aversion via mPFC output to the brainstem (Vander Weele et al., 2018). mPFC neurons that receive dopaminergic input could promote aversion in context specific manners by integrating contextual inputs and via with disynaptic inhibition decrease approach (Fig. 3; motif 4). With these potential circuit motifs in mind, we review the literature of the mPFC circuits that modulate social behaviors, drug-seeking behavior and anhedonia, as they represent complex behaviors that are mediated by mPFC and could be modulated or encoded via mixed selectivity.

3. mPFC circuits and dynamics flexibly modulate social behaviors

Over the past decade there has been an explosion of research related to how mPFC circuits and pathways modulate social behaviors. Although the hypothalamus and other subcortical circuits are crucial for generating social behaviors, the mPFC is well situated to integrate relevant information (social rank, memories, context) to modulate social behaviors. Individual social interactions are not all the same, they can be positive or negative, depending on the context (previous social history, social rank relationships). mPFC subpopulations that carry valence information can help guide the appropriate behavioral response during a social interaction. For mPFC to flexibly guide social behavior it must have a dynamic and plastic representation of social cues. We review recent studies that support a dynamic representation of social cues in the mPFC. In addition, to flexibly modulate social behaviors the mPFC must have the ability to both promote and inhibit social behaviors. In support of this idea, the mPFC has multiple distinct circuits that either promote or decrease sociability, and some that can be modulated by social experience (Challis, Beck, & Berton, 2014; Franklin et al., 2017; Zhou et al., 2017). Finally, with convergence of shared functions for valence-related and social processing, there is an overlap in the mPFC circuits that regulate sociability, fear and anxiety-like behavior (Felix-Ortiz, Burgos-Robles, Bhagat, Leppla, & Tye, 2016; Huang, Zucca, Levy, & Page, 2020), suggesting that the mPFC integrates negative valence information to decrease social exploration. We review the literature that supports a role of mPFC circuits in flexibly guiding social behavior (Fig. 4) from the lens of a potential interaction of valence encoding and social functions.

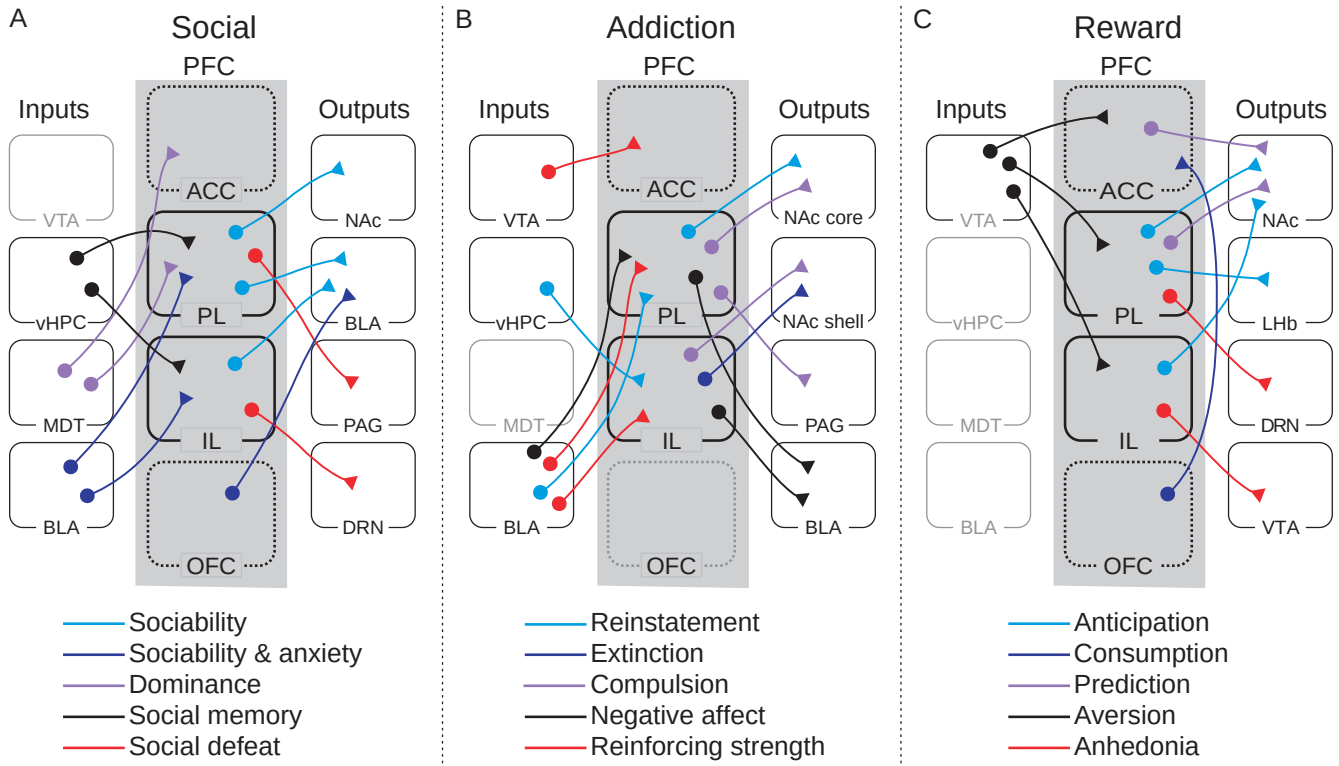

Fig. 4 See figure legend on next page.

3.1 mPFC social representation is dynamic and flexible

For the mPFC to flexibly guide social behavior a static representation of social cues could decrease the ability to flexibly modulate social behaviors. Across species, evidence points to the mPFC having a dynamic representation of social cues. In humans, the mPFC is activated in response to thinking of yourself or others (Seger, Stone, & Keenan, 2004), and the degree of social connections impacts the overlap in the mPFC representation (Courtney & Meyer, 2020). This study suggests that the mPFC social representation is dynamic and depends on social history. In mice, the mPFC represents the conspecifics as well, and mPFC single cell activity can be best predicted when taking into account both the behavior of the self and the other (Kingsbury et al., 2019). In addition, another study showed that mPFC cells can become responsive to social cues with repeated representation (Levy et al., 2019), further demonstrating that mPFC social representation is dynamic. An mPFC circuit that shows a flexible, and mixed selective, social representation is the prelimbic cells that project to the NAc, as they show spatial-social firing patterns (Murugan et al., 2017). Altogether, these studies show that mPFC social representation is not static and could evolve with the needs of the animal and changes in social history.

3.2 Distinct mPFC circuits bidirectionally control sociability

Our ability to socialize is important for survival and health (Cacioppo & Cacioppo, 2018; Matthews & Tye, 2019), and socializing is a complex process influenced by many of the traditional PFC functions such as

Fig. 4 mPFC circuits involved in social behaviors and reward processing. PFC neural circuits involved in social, addition, and reward behaviors. (A) PFC inputs from vHPC, MDT, and BLA implicated in social memory (black), dominance (purple), sociability and anxiety (dark blue). PFC outputs to the NAc, PAG, BLA, and DRN involved in sociability (light blue), social defeat (red), sociability and anxiety (dark blue). (B) PFC inputs from VTA, vHPC, and BLA implicated in reinforcing strength (red), reinstatement (light blue), and negative affect (black). PFC outputs to the NAc core, NAc shell, PAG, and BLA involved in reinstatement (light blue), compulsion (purple), extinction (dark blue), and negative affect (black). (C) PFC inputs from VTA implicated in aversion (black). PFC outputs to the NAc, LHb, DRN, and VTA involved in reward prediction (purple), reward consumption (dark blue) anticipation (light blue), and anhedonia (red). Subdivisions of the PFC: ACC, anterior cingulate cortex; PL, prelimbic; IL, infralimbic; OFC, orbitofrontal cortex. PFC projections/connections to brain regions: vHPC, ventral hippocampus; MDT, mediodorsal thalamus; BLA, basolateral amygdala; NAc, nucleus accumbens; NAc core; NAc shell; PAG, Periaqueductal gray; DRN, dorsal raphe nucleus; VTA, ventral tegmental area; LHb, lateral habenula.

decision-making, cognitive flexibility, memory and compulsive control. Recent optogenetic and chemogenetic studies have revealed that the mPFC has multiple subcortical outputs that modulate sociability and many of these circuits also play a role in valence encoding. Therefore, these mPFC circuits provide a mechanism to flexibly adjust social behavior depending on the potential rewards or dangers in the environment. A recent study showed that the dissociable roles of the infralimbic/prelimbic projections to the BLA in fear and anxiety (Adhikari et al., 2015) extend to sociability (Huang et al., 2020). Activity of PL → BLA cells decreased sociability while IL → BLA activity promoted sociability. Moreover, activation of PL → BLA cells that respond to negative stimuli (shock) was sufficient to see the decrease social preference (Huang et al., 2020), suggesting that negative valence cells are the same that modulate social preference. However, the PL → BLA circuit does not necessarily have a simple and static role in modulating sociability. Another study showed that optogenetic stimulation of PL → BLA neurons did not increase sociability when there was both a novel object and conspecific present (Murugan et al., 2017), supporting a dynamic role for PL → BLA neurons in which the exact context affects their function. Interestingly, the same study showed that PL → NAc stimulation resulted in decreased sociability in this behavioral paradigm (Murugan et al., 2017). Further evidence for a pro-social role of the IL → BLA circuit is that activating it mitigates the social behavioral effects of social defeat in subordinate, but not dominant, syrian hamsters (Dulka et al., 2020). It is of note that the IL → BLA mitigation was dependent on the social rank, as this further supports a non-static role of mPFC circuits in modulating social behaviors.

Common circuitry controls anxiety and social behaviors. Activation of the BLA input to mPFC both increased anxiety-like behavior and decreased sociability in a resident intruder assay (Felix-Ortiz et al., 2016). Importantly, the resident intruder assay is used as a measure of social anxiety in rodents since it is sensitive to anxiolytics (Calhoon & Tye, 2015; File & Animal, 1985). Humans and mice carrying the Val66Met allele (Chen et al., 2006; Li et al., 2019) show increased social anxiety. Moreover, in both humans and mice, social anxiety was linked to altered OFC-amygdala activity (Li et al., 2019). These studies support an interactive relationship between anxiety and social behaviors, and demonstrate that social behaviors can be inhibited due to anxiety signals via the PFC. Overall, mPFC circuits are well situated to modulate sociability bidirectionally to flexibly adjust social behaviors based on valence.

3.3 mPFC circuits change with social defeat and dominance

mPFC social representations are dynamic and change with social experience. What is the mechanism for this change in neural dynamics? One possibility is that there is plasticity in specific mPFC circuits with social experience. Consistent with this hypothesis, recent studies in mice show that mPFC circuits are sensitive to social defeat (Challis et al., 2014; Franklin et al., 2017) and dominance (Zhou et al., 2017).

Two mPFC projections to the brainstem are bidirectionally modulated by social defeat. After social defeat, optogenetic inhibition of the mPFC → DRN pathway rescued social defeat-induced changes in sociability (Challis et al., 2014). This study showed that specifically the ventral mPFC (IL) innervates GABAergic DRN cells, therefore potentially resulting in lower serotonin release which could mediate the social-affective changes induced by social defeat. On the other hand, social defeat decreased mPFC → dPAG connectivity and inhibition of the glutamatergic mPFC → dPAG pathway in non-defeated mice decreased social interaction (Franklin et al., 2017), suggesting that mPFC → dPAG is a pathway that can flexibly modulate sociability depending on social experience. Interestingly, a recent study showed that mPFC → dPAG neurons encode negative valence stimuli (shock) and promote aversion and anxiety-like behavior (Vander Weele et al., 2018). One possibility that could consolidate these seemingly opposing roles of the same circuit is that non-overlapping mPFC → dPAG neurons could be mediating the two distinct roles. Alternatively, the decrease in connectivity in the mPFC → dPAG pathway induced by social defeat could be a plasticity response due to overactivity in this subpopulation as it signals aversion.

An emerging field of the neural circuits underlying social dominance has shined light into the role of mPFC and the medial dorsal thalamus (MDT). Traditionally, the MDT → mPFC pathway has been linked to cognitive flexibility and spatial working memory (Bolkan et al., 2017; Hunt & Aggleton, 1991; Parnaudeau et al., 2013). A recent study showed that social dominance increases plasticity in the MDT-mPFC pathway and LTP induction in this synapse causes instant winning during social competition (Zhou et al., 2017). An additional study showed that MDT was required for the formation of the social hierarchy (Nelson et al., 2019) providing further support that plasticity in the thalamocortical pathway is important for social dominance. Altogether, these studies demonstrate that social experience induces synaptic plasticity in distinct mPFC circuits, thereby highlighting the dynamic role of mPFC circuits in modulating social behaviors.

3.4 Mixed selectivity in social behaviors

Social information is multisensorial and complex. Even in the simplest rodent behavioral assay the presence of another mouse is an olfactory, visual, and auditory cue. In addition to being multisensorial, social behavior is influenced by social experience, context, and internal state. Therefore, any social interaction has multiple parameters and the prefrontal cortex could potentially encode more information by having mixed selectivity to multiple cues and parameters of the social interaction. We see an example of this mixed selectivity in how PL → NAc neurons only encode spatial location when another animal is in the environment, thus demonstrating that mixed selectivity can be observed in a specific subpopulation of neurons (Murugan et al., 2017). In addition, we have reviewed that there is an overlap of the mPFC circuits that mediate valence and social behaviors. An example of this scenario is seen in the recent study by Huang et al., where the same PL → BLA neurons that encode shock modulate sociability. This overlap of mPFC circuits that mediate valence with mPFC circuits that modulate social behavior provides the possibility that the same mPFC neurons may be responding to a combination of threat level, reward assessment, and social stimuli. Mixed selectivity could provide a computational way to encode these parameters more efficiently and to allow the mPFC to flexibly modulate social behaviors.

4. The mPFC is involved in addictive and compulsive behavior

Drug addiction is a chronic, relapsing disorder characterized by the compulsion to seek and take drugs despite associated negative consequences. Addictive drugs are intrinsically rewarding and reinforcing and thus represent positive valence that confers incentive salience (Berridge & Robinson, 2016). Following excessive drug use, drug-associated positive valence has been observed to be both heightened and blunted (Ahmed & Koob, 1998; Grigson & Twining, 2002; Volkow et al., 1997). Heightened drug-associated positive valence can lead to anhedonia, or the loss of pleasure towards non-drug related rewarding stimuli, driving continual drug seeking and abandonment of other rewarding behaviors (e.g., social interaction) (Grigson & Twining, 2002). In other cases, heightened drug-associated positive valence can lead to sensitization or increased positive valence towards other rewarding stimuli (e.g., sucrose) (Bechara, Dolan,

& Hindes, 2002; Fiorino & Phillips, 1999; Goldstein et al., 2007; Nocjar & Panksepp, 2002; Taylor & Horger, 1999; Wyvell & Berridge, 2001). Overactivation of reward pathways in drug addiction leads to concurrent, homeostatic activation of antireward or stress pathways mediating negative reinforcement driving compulsive drug use to alleviate negative internal states created by drug abstinence (Koob & Le Moal, 2008; Solomon, 1980), suggesting that negative valence processing may be particularly important in the development and maintenance of drug addiction. Therefore, both positive and negative valence-associated circuits are likely to be critical for distinct processes in the transition to drug addiction. We review the literature on mPFC circuits involved in drug addiction from the perspective of valence encoding (Fig. 4) and finally integrate the computational framework of mixed selectivity to explain how the mPFC flexibly regulates drug related decisions.

4.1 mPFC-NAc projectors mediate drug reinstatement and extinction

Evidence from clinical and preclinical studies point to a prominent role of the mPFC in addiction (Franklin et al., 2002; George & Koob, 2013; Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014; Van den Oever, Spijker, Smit, & De Vries, 2010; Volkow & Fowler, 2000; Volkow, Fowler, & Wang, 2003). Several projection-specific mPFC neurons regulate drug seeking and extinction. The PL and IL subregions of the mPFC predominantly project to the NAc core and shell, respectively (Sesack, Deutch, Roth, & Bunney, 1989), and largely play distinct functional roles in addiction-related behaviors (Moorman, James, McGlinchey, & Aston-Jones, 2015; Peters, Kalivas, & Quirk, 2009). The PL → NAc core is necessary for cue-induced reinstatement whereas the IL → NAc shell is critical for drug extinction. PL neurons projecting to the NAc core are activated by cocaine cues during reinstatement, which positively correlate to cocaine seeking action (McGlinchey, James, Mahler, Pantazis, & Aston-Jones, 2016), suggesting the recruitment of this pathway in drug seeking. Indeed, ablation and silencing of PL → NAc core decreases drug primed- and cue-induced reinstatement of cocaine seeking (Kerstetter et al., 2016; Stefanik et al., 2013; Stefanik, Kupchik, & Kalivas, 2016), consistent with the roles of PL and NAc in drug reinstatement (Kalivas, Volkow, & Seamans, 2005), and sensitivity to an alcohol and nicotine complex interoceptive cues (Randall, McElligott, & Besheer, 2020). In contrast to the PL → NAc core pathway, chemogenetic activation of IL → NAc shell circuit decreases cue-induced reinstatement of cocaine seeking after

extinction training (Augur, Wyckoff, Aston-Jones, Kalivas, & Peters, 2016), suggesting a role of the IL → NAc shell in extinction memory. Altogether, these studies suggest that the mPFC → NAc pathway may represent the learned positive valence associated with drug cues.

Notably, with increasing time in abstinence following prolonged drug self-administration, there is a parallel increase in drug cravings, a phenomenon termed *incubation (*Gawin & Kleber*, 1988;* Grimm, Hope, Wise, & Shaham, 2001*)*. How drug abstinence alters the representation of drug-associated cues/contexts was recently uncovered, providing insight into cocaine incubation. Cameron, Murugan, Choi, Engel, & Witten (2019) found that IL → NAc shell neurons encode spatial location in a drug context, and the percent of spatial encoding neurons is decreased following prolonged abstinence, suggesting a reduced representation of the drug context. IL → NAc shell projectors exhibit an overall inhibition in activity prior to drug seeking action, which is also reduced following a prolonged period of abstinence. Optogenetic stimulation of IL terminals in the NAc shell decreases drug seeking action following both acute and prolonged abstinence periods (Cameron, et al., 2019). These findings suggest that decreased representation of drug-related context during abstinence in the IL → NAc shell, an extinction-related circuit, may underlie incubation of cocaine craving. The involvement of mPFC projectors in cue-induced, context-induced, and incubation requires the continual, dynamic representation of drug associated cues. We speculate that mixed selectively properties of the mPFC enable this representation of drug associated cues across several timescales.

4.2 Reprogramming corticostriatal circuits for therapeutic plasticity

Drug exposure induced synaptic plasticity in corticostriatal circuits presents a potential avenue for neural circuit reprogramming for therapeutic intervention. In line with the dichotomous corticostriatal pathways, Ma et al. (2014) found that prolonged cocaine abstinence activates drug-induced silent synapses in PL and IL terminals in the NAc core and shell, respectively, through distinct mechanisms. Using an optogenetic stimulation protocol to induce long-term depression (LTD), essentially reversing the activation of cocaine-induced silent synapses in the PL → NAc core and IL → NAc shell led to decreases and increases in cocaine incubation, respectively, which similarly regulates alcohol-seeking behavior as well (Ma et al., 2014; Ma et al., 2018). In addition, using a similar optogenetic LTD stimulation approach, Pascoli et al. (2014) found that reversing the observed

cocaine-induced plasticity simultaneously at both the mPFC and vHPC terminals in the NAc shell abolished cue-induced reinstatement of drug-seeking, which persisted for a week (Pascoli et al., 2014). The enduring inhibition of drug-seeking by LTD-induction highlights the potential for reprogramming mPFC circuits for addiction treatment. Interestly, selective manipulation of mPFC terminals in the NAc impairs discrimmination between the drug-associated active lever and inconsequential inactive level without altering drug seeking (Pascoli et al., 2014), suggesting that cocaine-evoked plasticity in mPFC → NAc supports the learned association between action and drug delivery. Beyond corticostriatal circuits, mPFC neurons projecting to the laterodorsal tegmental nucleus (LDT) have been implicated in reward-associated behaviors (Coimbra et al., 2019; Kamii et al., 2015; Lammel et al., 2012; Xiao et al., 2016). mPFC inactivation prevents cocaine-induced plasticity in the LDT (Kurosawa, Taoka, Shinohara, Minami, & Kaneda, 2013), suggesting the importance of mPFC → LDT in cocaine-related positive valence—begging a causal investigation for mPFC → LDT involvement in the drug-associated behavior. Together, drug-induced plasticity is an important mechanism by which mPFC circuits regulate addiction-related behavior, and remodeling of drug-induced plasticity in discrete mPFC circuits holds therapeutic promise for drug relapse.

4.3 Inputs to the mPFC provide valence and context to modulate addiction-related behaviors

Subcortical inputs carrying diverse stimuli-related functional signals are integrated within the mPFC influencing behavior. In particular, valence and context related information is sent to the mPFC and modulates drug reinforcement and drug-seeking behavior.

The BLA sends dense projections to the mPFC that regulate anxiety-like behavior, social interaction, fear learning, and has been proposed to rapidly process and route negative valence information to the mPFC (Burgos-Robles et al., 2017; Felix-Ortizet al., 2016; Klavir, Genud-Gabai, & Paz, 2013). In line with this, Dong, Taylor, Wolf, & Shaham (2017) found that ablation of BLA neurons projecting to the mPFC (BLA → mPFC) increases motivation for alcohol consumption (Dong, et al., 2017), suggesting that BLA → mPFC may limit the reinforcing strength of alcohol consistent with its role in negative valence. It is important to note that BLA → mPFC neurons innervate neighboring BLA neurons as well as send collaterals to other brain regions (Beyeler et al., 2016, 2018), thus it is yet to be determined if the inputs to the mPFC directly mediate alcohol seeking behavior. Contrasting

findings from Stefanik & Kalivas (2013) show that optogenetic inhibition of BLA terminals in the PL subdivision of the mPFC inhibits cue-induced reinstatement of cocaine seeking (Stefanik & Kalivas, 2013). Although these studies used different behavioral paradigms, the findings suggest that BLA → mPFC may differentially regulate drug seeking behavior depending on the drug and context. The demonstrated role of the BLA → mPFC pathway in regulating drug seeking and negative valence suggests a potential role of this circuit in compulsive drug use, although this remains to be explored.

The HPC has been implicated in drug reinstatement, and its connectivity with the mPFC regulates relapse to extinguished fear, context-guided memory, and drug-associated cognitive deficits (Fuchs et al., 2005; Kutlu & Gould, 2016; Marek et al., 2018; Place, Farovik, Brockmann, & Eichenbaum, 2016; Rogers & See, 2007; Wang, Jin, & Maren, 2016). Wang et al. found that vHPC-IL projections are activated by context-induced reinstatement of heroin seeking, and chemogenetic inhibition of vHPC-IL decreased heroin seeking (Wang et al., 2018). Moreover, pharmacological manipulation studies show that D1R and D2R signaling in the vHPC → mPFC are important for the acquisition and retrieval of morphine contextual memory depending on opiate exposure history (Wang et al., 2019). However, causal implication of the vHPC → mPFC circuit in drug-associated contextual memory remains to be tested.

The mPFC also receives afferent dopamine projections from the VTA. Interestingly, Narita et al. (2010) found that electrical or μ-opioid receptor agonist (DAMGO) stimulation of the VTA increases dopamine release in the ACC. VTA infusion of DAMGO induces a conditioned place preference that is significantly reduced by chemical lesion of dopamine terminals in the ACC (Hitora-Imamura et al., 2015). These findings suggest that VTA → ACC signals positive valence information related to the reinforcing effects of opioids, which is in opposition to the identified role of VTA → mPFC in aversion (Hitora-Imamura et al., 2015; Lammel et al., 2012; Mantz, Thierry, & Glowinski, 1989; Vander Weele et al., 2018). Alternatively, it is possible that VTA dopamine is necessary for the learned association between drug and context, consistent with the proposed role of mPFC dopamine transients in learning rather than valence (Popescu, Zhou, & Poo, 2016).

While limited studies have directly examined the impact of inputs to the mPFC in addiction-related behaviors, these studies point to a role of BLA, HPC, and VTA inputs to the mPFC in both negative and positive valence aspects of drug reinforcement and context influencing drug seeking

behavior. Convergence of these diverse inputs could provide a circuit motif that promotes mixed selectivity in mPFC during drug addiction (Fig. 3).

4.4 Corticoamygdalar circuits mediate abstinence-induced negative affect

Negative affective states created by drug abstinence provide a strong motivational drive to use drugs, contributing to negative reinforcement processes underlying the transition and maintenance of drug dependence (Ahmed & Koob, 1998; Koob & Le Moal, 2008). Multiple studies have now implicated corticoamygdalar circuits in regulating drug abstinence-induced negative affect, consistent with the role of corticoamygdalar circuits in negative valence processing (Burgos-Robles et al., 2017; Felix-Ortiz et al., 2016). McGinnis, Parrish, Chappell, Alexander, & McCool (2020) found that withdrawal from chronic intermittent alcohol exposure strengthens PL → BLA while weakening IL → BLA connectivity. Chemogenetic inhibition of PL terminals in the BLA decreased withdrawal-induced anxiety-like behavior (McGinnis, et al., 2020), highlighting the therapeutic potential of synaptic remodeling in PL → BLA circuits. In line with this, Zhao et al. (2017) found that morphine withdrawal-associated contextual cues activate the mPFC → BLA projectors, suggesting that this circuit may receive contextual information. Chronic morphine exposure increased D1R expression in mPFC → BLA terminals and reversing this D1R overexpression decreased conditioned morphine withdrawal place aversion (Zhao et al., 2017). In addition, amygdala inputs to the mPFC also regulate morphine withdrawal-associated negative affect, as optogenetic inhibition of BLA terminals in the PL inhibits conditioned context-induced place aversion by morphine withdrawal (Song et al., 2019). To date, corticoamygdalar circuits remain the only mPFC circuit directly implicated in regulating drug-associated negative affect. These findings highlight the importance of corticoamygdalar circuitry for representation of negative valence during drug withdrawal states contributing to negative reinforcement driving continual, excessive drug use.

4.5 Cortical regulation of compulsive drug use via striatal and brainstem projections

A defining feature of drug addiction is the compulsion to seek and take drugs despite associated negative consequences. Punishment-resistant drug use is assessed by the introduction of footshock or adulteration of the drug

(e.g., alcohol) with the bitter-tastant quinine during drug seeking or taking. In the face of competing rewarding and aversive stimuli, the mPFC is recruited (Burgos-Robles et al., 2017). Indeed, IL neurons, and to a lesser degree PL neurons, encode alcohol seeking action, which is significantly diminished during sessions with punishment (Halladay et al., 2020). In addition, mPFC neurons encode aborts (i.e., when lever approaches are quickly aborted) during punished alcohol seeking and in subsequent unpunished alcohol seeking (Halladay et al., 2020). Of note, encoding of alcohol seeking action and aborts are represented by distinct IL ensembles (Halladay et al., 2020), potentially delineated by anatomical projection although remains to be determined. Causal optogenetic inhibition of IL increases compulsive alcohol seeking, and manipulation of PL bidirectionally regulates compulsive cocaine seeking (Chen et al., 2013). Punishment induced neuroplastic adaptations in IL inputs to NAc shell D1R-expressing neurons, and optogenetic silencing of IL → NAc shell, but not IL → BLA, decreases the effects of punishment on alcohol seeking, suggesting that IL → NAc may encode aborts (Halladay et al., 2020). Consistent with the role of the PL in compulsive cocaine seeking, optogenetic inhibition of PL → NAc core decreases compulsive alcohol intake, but not unpunished alcohol intake, which is dependent on hyperpolarization-activated NMDA receptors (Seif et al., 2013). Interestingly, activation of shock-encoding PL → NAc suppressed reward seeking, suggesting that distinct subpopulations within PL → NAc projectors may differentially regulate reward seeking (Kim et al., 2017). Consistent with the role of the mPFC in processing both reward and aversion, discrete mPFC circuits integrate punishment and drug-associated positive valence to flexibly regulate compulsive drug use.

In addition, mPFC → PAG neurons selectively route aversive-stimuli information (Vander Weele et al., 2018), and Siciliano et al. found that activity patterns in mPFC neurons projecting to the PAG during initial alcohol exposure is predictive of later development of compulsive alcohol drinking behavior (Siciliano et al., 2019). Using machine learning, the authors show that mPFC → PAG neural activity during compulsive alcohol drinking was predictive of whether mice would drink or not drink during the subsequent opportunity to drink (Siciliano et al., 2019), consistent with the mPFC → PAG neurons routing aversive-stimuli information. Moreover, optogenetic manipulation of mPFC terminals in the PAG bidirectionally compulsive alcohol drinking, respectively, but not unpunished alcohol drinking (Siciliano et al., 2019). This study highlights the importance of

negative valence processing by the mPFC in regulating compulsive drug taking behavior. Moreover, it suggests that negative valence-related mPFC circuits are important for negative reinforcement and compulsive aspects of drug addiction.

These data highlight a specific role of mPFC → NAc and mPFC → PAG circuits in compulsive drug seeking and taking, and the potential of these circuits to encode both drug-associated positive and punishment-associated negative valence. Mixed selective mPFC neurons in these pathways may be critical in simultaneously encoding reward and punishment associated contingencies for decision making in seeking drugs despite associated consequences.

4.6 Integration of circuits and mixed selectivity in drug addiction

How do these discrete, seemingly static circuits regulate the decision to seek and take drugs? Mixed selectivity properties of the mPFC allow for the complex integration of a multitude of parameters enabling the consequent orchestration of behavior. Several factors influence the decision to use drugs including past rewarding or aversive experiences, drug cravings triggered by drug-associated contexts/cues, internal emotional states, and predictions of future consequences. Specific contexts (i.e., environmental, emotional, internal state, recent prior experience) can elicit cravings and trigger relapse in rodents, primates, and humans (Chaudhri, Sahuque, & Janak, 2008; Fox, Bergquist, Hong, & Sinha, 2007; Litt & Cooney, 1999; Perry, Zbukvic, Kim, & Lawrence, 2014; Reid, Flammino, Starosta, Palamar, & Franck, 2006; Seo et al., 2013; Spealman et al., 2004; Zironi, Burattini, Aicardi, & Janak, 2006), highlighting a conserved behavioral adaptation contributing to addiction. The context in which drug-associated cues are encountered also influence the degree to which drug cues elicit cravings and relapse (Hyman, 2005). Context may modulate drug-associated valence altering drug cue reactivity. For example, during hunger states food-associated positive valence may exceed that of drugs consequently transiently diminishing drug-associated positive valence. The brain continuously assesses this rich multidimensional information to flexibly regulate the decision to use drugs.

As mentioned, the mPFC has mixed selectivity properties enabling simultaneous representation of diverse parameters within and across contexts (Fig. 2). This provides a new conceptual framework in which to understand addiction-related behavioral adaptations such as context-dependent drug craving. Exposure to drug-associated cues under various contexts may

trigger activity in mixed selective mPFC neurons encoding salient drug cues and contexts, dynamically shifting population level encoding of the decision to use drugs. For example, mixed selective neurons receiving contextual information from HPC inputs and negative valence information from VTA inputs (Hitora-Imamura et al., 2015; Lammel et al., 2012; Mantz et al., 1989; Vander Weele et al., 2018), may flexibly shift the representation of negative internal states or punishment under various contexts in response to fluctuating dopamine levels to alter motivation for drugs. In line with this idea, mPFC dopamine is necessary for drug relapse under certain conditions (Capriles, Rodaros, Sorge, & Stewart, 2003; James, McGlinchey, Vattikonda, Mahler, & Aston-Jones, 2018; McFarland, Davidge, Lapish, & Kalivas, 2004; Wang et al., 2019). Simultaneous representation of drug reward-associated context and drug abstinence-associated negative internal states may bias population encoding to increase the decision to seek and take drugs despite associated negative consequences underlying drug incentive salience.

Diverse input (e.g., valence- and context-related) to mixed selective mPFC neurons that project to several downstream brain regions may be a mechanism by which hard-wired circuits flexibly direct behavior. Indeed, overlapping mPFC circuits regulating several addiction-related behaviors allow for multiple avenues by which mPFC mixed selective neurons may direct the decision to use drugs. Conceptual integration of circuits and the computational model of mixed selectively provides a new framework for understanding drug addiction.

5. The mPFC as a major component in reward processing

5.1 mPFC circuits involved in "wanting" and "liking"

In reward processing, pleasure is categorized into a anticipatory phase and consummatory phase (Berridge, 2004). During the anticipatory phase, referred to as "wanting," the motivation to receive a reward elicits pleasure (Berridge, 2004); thereby promoting appetitive behaviors that includes foraging for food, sex, and social interactions. Whereas in the consummatory phase, also described as "liking," pleasure is induced by hedonic impact of a reward via initial sensory stimuli (Berridge, 2004). Here we review recent literature describing the role of PFC circuits in motivation and anticipation during reward seeking and consumption (Fig. 4).

Specific mPFC projections participate in anticipatory pleasure. For instance, mPFC layer 5 projection neurons to the NAc (Gabbott et al., 2005)—a major site for reward detection and reward learning (Castro & Berridge, 2014; Day & Carelli, 2007; Day, Roitman, Wightman, & Carelli, 2007)—inhibit reward-seeking behavior in response to aversive stimuli (Kim et al., 2017). For instance, Kim et al identified a specific subset of mPFC → NAc projecting neurons that are recruited in response to electrical shock and are involved in suppressing reward-seeking behavior (Kim et al., 2017). Another downstream target involved in anticipation and reward-seeking behavior is the lateral habenula (LHb) (Benekareddy et al., 2018; Matsumoto & Hikosaka, 2007, 2009; Warden et al., 2012). In rhesus monkeys, the LHb is activated upon presentation of neutral stimuli and punishment, but is inhibited upon reward presentation (Matsumoto & Hikosaka, 2007, 2009). Interestingly, photostimulation of mPFC → LHb in rats significantly reduced mobility in the forced swim task (FST), suggesting a lack of motivated-behavior or a passive coping strategy, in contrast to mPFC → DRN activation that increased kicking and promoted an active coping strategy(Warden et al., 2012). The FST is a commonly used assay to examine anhedonia in rodents, as immobility is a measurement of behavioral despair and mimics depressive-like phenotypes. Nevertheless, these neural circuit studies highlight the diverse pathways that control reward seeking-behavior and motivated behavior.

The OFC, a subregion of the PFC, acts as a primary mediator of consummatory pleasure. It integrates multiple sensory inputs, conveying pleasure sensation in response to gustatory, tactile, visual, olfactory and social stimuli (Grabenhorst & Rolls, 2011), and encodes reward reinforcement and reward prediction via midbrain dopaminergic neurons (Berridge & Kringelbach, 2008; Sul, Kim, Huh, Lee, & Jung, 2010; Takahashi et al., 2009). In a recent study, Jennings et al. identified distinct OFC neuronal ensemble populations which responded to caloric consumption or social interaction, indicative of consummatory pleasure (Jennings et al., 2019). In this study, single-cell activation of social cells suppressed feeding behavior, indicating microcircuit level changes within the OFC that are recruited in response to select reward stimuli. However, whether these OFC neuronal ensembles are affected in specific contexts remains to be investigated.

5.2 mPFC circuits involved in reward-prediction and reward learning

Reward is directly implicated in hedonic pleasure and plays a major role in everyday decision-making processes that can influence survival, lifestyle, or

wellbeing. The value of a reward is often described as the neuroeconomic benefit received from a stimulus and can be transient or sustained over long periods of time. Therefore, the reward is evaluated, and the value is determined depending on the salience and/or retrieved memories from prior experiences.

Dopamine (DA) is historically best known for being the principal neurological substrate involved in hedonic pleasure and it is responsible for regulating reward value, reward outcome and motivation (Beyeler et al., 2016; Dong et al., 2017; Klavir et al., 2013). This is predominantly mediated via DA neurons in the VTA of the midbrain, however, the role of VTA DA is heterogenous and depends on the specific downstream circuits (Lammel et al., 2012; Lammel, Ion, Roeper, & Malenka, 2011; Lammel, Tye, & Warden, 2013; Vander Weele, Siciliano, & Tye, 2018). Dopamine in the PFC has been implicated in processing negatively valenced stimuli (Vander Weele et al., 2018), and can produce avoidance (Gunaydin et al., 2014), but is suggested to be a major component in reward prediction (Schultz, Dayan, & Montague, 1997). This suggests that DA modulates mPFC encoding of both positive and negative valence in behavior. Many questions remain unanswered; are there mPFC mixed selectivity neurons that encode for opposite valence? And does DA alter their activity?

The ACC, along with the OFC, encodes reward predictive cues and subjective pleasure (Behrens, Hunt, Woolrich, & Rushworth, 2008; Grabenhorst & Rolls, 2011; Kennerley, Dahmubed, Lara, & Wallis, 2009; Kennerley & Wallis, 2009; Kim, Hwang, & Lee, 2008; Rolls & Grabenhorst, 2008), and is highly active when reward outcome influences decision-making processes (Walton, Devlin, & Rushworth, 2004). Specifically, optogenetic inhibition of ACC or prelimbic projections to the dorsomedial striatum increases reward-seeking behavior during conflict (Friedman et al., 2015). Other studies linked the mPFC → NAc pathway to reward prediction and reward learning. For instance, studies in rodents showed that mPFC → NAc projection neuron activity is amplified in response to reward-predictive cues following reward learning and can induce reward-seeking behavior (Otis et al., 2017). In contrast, activating mPFC → PVT (paraventricular nucleus of the thalamus) neurons suppresses conditioned reward seeking behavior (Otis et al., 2017), and is time-dependent in fear learning, indicating the dynamic role within this pathway. However, it remains to be seen whether the mPFC neuronal projecting populations involved in reward prediction are altered in response to context-specific changes.

5.3 mPFC activity disrupted during anhedonia

Anomalous mPFC activity has been implicated in neuropsychiatric disorders such as major depressive disorders (MDD) and schizophrenia (SCZ). Anhedonia is described as the inability to experience pleasure or hedonic feeling, affecting both consumption and anticipatory reward values, and is observed in both MDD and SCZ (Lee, Jung, Park, & Kim, 2015; Pizzagalli & Depression, 2014). The etiology of anhedonia is linked to disruptions within the brain reward pathways due to dysregulation of dopamine transmission (Chaudhury et al., 2013; Harvey, Pruessner, Czechowska, & Lepage, 2007; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Tye et al., 2013) and anomalous mPFC neural activity (Ferenczi et al., 2016; Kim et al., 2017; Warden et al., 2012). For instance, optogenetic studies in rodents revealed that increasing mPFC activity in glutamatergic projection neurons causes a significant decrease in sucrose consumption and social interaction, indicative of a depressive-like phenotype (Ferenczi et al., 2016). Accordingly, in human imaging studies, depressed patients revealed elevated activity in the subgenual ACC of the PFC, which was alleviated following deep brain stimulation (Mayberg et al., 2005). Similarly, deep brain stimulation of the ACC in depressed patients improved depressive-like symptoms in the refractory treatment period (Johansen-Berg et al., 2008; Schlaepfer et al., 2008). Contrastingly, other imaging studies in depressed patients revealed a reduction in PFC activity (Galynker et al., 1998), which may be attributable to a reduction in glutamatergic transmission due to a decrease in the number of synapses (Duman, Sanacora, & Krystal, 2019; Kang et al., 2012). These studies highlight a discrepancy in the literature describing PFC neural activity regarding anhedonia. What could underlie these discrepancies? It is possible that projection-specific neuronal populations are differentially altered during anhedonia, thus resulting in opposing distinct changes in mPFC neural activity.

5.4 mPFC projecting neurons involved in anhedonia

mPFC projection target regions were identified to be involved in anhedonia. For instance, acute optogenetic stimulation of mPFC-projecting neurons in the dorsal raphe nucleus (DRN) in rats increased mobility in the forced swim task, promoting motivation and active coping strategy (Warden et al., 2012). This study highlighted the importance of circuit-specific studies, as acute optogenetic stimulation of the mPFC caused no significant changes in mobility. The mPFC → DRN pathway is also involved

in social interaction, as photoinhibition of this circuit prevents social withdrawal following a social defeat paradigm (Challis, et al., 2014). The DRN, a major target in depression (Maier, 2015; Sf & Lr, 2005), consists of both serotonergic and GABAergic neurons that primarily receive inputs from PL projections onto GABAergic interneurons (Peyron, Petit, Rampon, Jouvet, & Luppi, 1997; Vertes, 2004), which indirectly inhibits serotonergic neurons (Jankowski & Sesack, 2004). Interestingly, it was recently shown that both serotonergic and GABAergic neurons in the DRN exhibit context-specific changes in negative environments (Seo et al., 2019). It is likely mPFC-DRN projections change depending on mood or during disease states; however, these hypotheses have yet to be investigated.

The VTA is another major region implicated in anhedonia, and can be regulated via top-down connections from cortical regions that modulate DA activity (Chaudhury et al., 2013; Ferenczi et al., 2016; Tye et al., 2013). Accordingly, the VTA receives sparse projections from the mPFC that innervate both GABA and DA neurons and have no preferential input (Beier et al., 2015; Carr & Sesack, 2000a). Interestingly, activating the IL-PFC reduced VTA DA excitability in rats, specifically in medial VTA neurons that were most sensitive to chronic mild stress (Moreines, Owrutsky, & Grace, 2017). It is likely mPFC projections strongly influence VTA DA activity attributable to anhedonia. However, whether there are differential effects of mPFC projections onto VTA DA and GABAergic neurons remains to be understood.

5.5 Mixed selectivity neurons during anhedonia

The PFC, as a higher-order processing center, is highly adaptable and dynamic. We propose that PFC function is compromised during anhedonia which may limit flexibility. For instance, human fMRI studies of MDD patients showed a marked decrease in PFC activity that is likely linked to glutamatergic dysconnectivity (Abdallah et al., 2017; Murrough, Abdallah, & Mathew, 2017). This corroborated previous findings that revealed PFC hypofrontality within MDD patients contribute to the negative symptoms of depression (Galynker et al., 1998). We suggest that during anhedonia, mixed selectivity neurons have a decreased capacity to encode reward due to changes in internal homeostasis. Accordingly, we expect an overall reduction in the activity of PFC mixed selectivity projections neurons, consistent with the observed decrease in PFC neural activity in MDD patients that lead to impairments in anticipation and reward consumption.

Additionally, mixed selectivity neurons may leverage axonal collateralization and bias preferential outputs onto specific neuronal populations. For instance, mPFC neurons innervate both GABA and DA neurons in the VTA, and receive reciprocal connections from both cell types (Carr & Sesack, 2000a, 2000b). The mPFC mixed selectivity neurons could provide preferential inputs that influence the postsynaptic response on specific cell types of the VTA that lead to differential behavioral outcomes. Indeed, we suggest postsynaptic gating mechanisms via axo-axonal inhibition, intrinsic excitability, and convergent inputs modulate the mixed selectivity outputs (Fig. 3). Accordingly, we propose that within an anhedonic state, changes in postsynaptic gating mechanisms decrease the ability to promote reward in a cell-type specific and brain region-specific manner. For example, changes in postsynaptic gating could shift mixed selectivity mPFC-VTA neurons to preferentially modulate VTA GABAergic neurons leading to an increase in the postsynaptic response. The increase in VTA GABAergic neuron activity would cause an inhibition in VTA DA release leading to depressive-like phenotypes. Altogether, this theoretical model would imply mPFC mixed selectivity neuronal output activity is tuned during anhedonia that would lead to deficits in anticipatory and consummatory pleasure.

6. Summary

In summary, we provide this review of the current state of PFC research to support the widely-appreciated role of the PFC in higher-order cognitive functions by highlighting the role of PFC ensembles and circuitry in mediating emotional processing and the cognitive appraisal of subcortically-mediated emotional processes in the context of mood disorders, addiction, and social behaviors. In addition to diversification of scope in function, we confront the growing chasm between the systems-level focus on the ensemble dynamics with flexible functions of individual "mixed selectivity" neurons (which point to the *ensemble* as the functional unit), and the circuit-level focus on the on the circuit components of input-output architectures and wiring diagrams (that point to the "hard-wired" *circuit component* as the functional unit). Moving forward, we anticipate the development of novel computational models for PFC function that may unite these perspectives (Tsuda, Tye, Siegelmann, & Sejnowski, 2020). At this point in the field with these rapidly diverging subfields, we are in need of a cohesive, integrative model that reconciles these contrasting viewpoints and ushers us back into a converging trajectory.

While perspectives will continue to diversify, cross-pollination across subfields of research will only enhance our understanding of the most uniquely-evolved structure in the human brain, and therefore ourselves.

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Competing interest

The authors report no competing interest or biomedical financial interests.

Author contributions

All authors contribute to conception, writing, figure making and editing/revising.

References

Abdallah, C. G., et al. (2017). Prefrontal connectivity and glutamate transmission: relevance to depression pathophysiology and ketamine treatment. *Biological psychiatry. Cognitive Neuroscience and Neuroimaging*, *2*, 566–574.

Abimbola, S., & Awolowo, O. (2006). The white cut: Egas Moniz, lobotomy, and the Nobel prize. *BMJ*, *332*.

Adhikari, A., et al. (2015). Basomedial amygdala mediates top-down control of anxiety and fear. *Nature*, *527*, 179–185.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature*, *372*, 669–672.

Ahmed, S. H., & Koob, G. F. (1998). Transition from moderate to excessive drug intake: Change in hedonic set point. *Science*, *282*, 298–300.

Aleyasin, H., Flanigan, M., & Russo, S. J. (2018). Neurocircuitry of aggression and aggression seeking behavior: Nose poking into brain circuitry controlling aggression. *Current Opinion in Neurobiology*, *49*, 184–191.

Allsop, S. A., Vander Weele, C. M., Wichmann, R., & Tye, K. M. (2014). Optogenetic insights on the relationship between anxiety-related behaviors and social deficits. *Frontiers in Behavioral Neuroscience*, *8*, 241.

Allsop, S. A., et al. (2018). Corticoamygdala transfer of socially derived information gates observational learning. *Cell*, *173*, 1329. 1342.e18.

Anderson, S. W., Barrash, J., Bechara, A., & Tranel, D. (2006). Impairments of emotion and real-world complex behavior following childhood- or adult-onset damage to ventromedial prefrontal cortex. *Journal of the International Neuropsychological Society*, *12*, 224–235.

Anderson, S. W., et al. (2007). The earliest behavioral expression of focal damage to human prefrontal cortex. *Cortex*, *43*, 806–816.

Augur, I. F., Wyckoff, A. R., Aston-Jones, G., Kalivas, P. W., & Peters, J. (2016). Chemogenetic activation of an extinction neural circuit reduces cue-induced reinstatement of cocaine seeking. *Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *36*, 10174–10180.

Bechara, A., Damasio, H., & Damasio, A. R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cereb. Cortex N. Y. N*, *1991*(10), 295–307.
Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, *50*, 7–15.
Bechara, A., Dolan, S., & Hindes, A. (2002). Decision-making and addiction (part II): Myopia for the future or hypersensitivity to reward? *Neuropsychologia*, *40*, 1690–1705.
Behrens, T. E. J., Hunt, L. T., Woolrich, M. W., & Rushworth, M. F. S. (2008). Associative learning of social value. *Nature*, *456*, 245–249.
Beier, K. T., et al. (2015). Circuit architecture of VTA dopamine neurons revealed by systematic Input-output mapping. *Cell*, *162*, 622–634.
Benekareddy, M., et al. (2018). Identification of a corticohabenular circuit regulating socially directed behavior. *Biological psychiatry*, *83*. https://pubmed.ncbi.nlm.nih.gov/29336819/.
Berridge, K. C. (2004). Motivation concepts in behavioral neuroscience. *Physiology & Behavior*, *81*, 179–209.
Berridge, K. C., & Kringelbach, M. L. (2008). Affective neuroscience of pleasure: Reward in humans and animals. *Psychopharmacology*, *199*(457–480).
Berridge, K. C., & Robinson, T. E. (2016). Liking, Wanting and the Incentive-Sensitization Theory of Addiction. *The American Psychologist*, *71*, 670–679.
Beyeler, A., et al. (2016). Divergent routing of positive and negative information from the amygdala during memory retrieval. *Neuron*, *90*, 348–361.
Beyeler, A., et al. (2018). Organization of valence-encoding and projection-defined neurons in the basolateral amygdala. *Cell Reports*, *22*, 905–918.
Blair, R. J. R., & Cipolotti, L. (2000). Impaired social response reversal. A case of 'acquired sociopathy'. *Brain: A Journal of Neurology*, *123*, 1122–1141.
Bolkan, S. S., et al. (2017). Thalamic projections sustain prefrontal activity during working memory maintenance. *Nature Neuroscience*, *20*, 987.
Bossert, J. M., et al. (2011). Ventral medial prefrontal cortex neuronal ensembles mediate context-induced relapse to heroin. *Nature Neuroscience*, *14*, 420–422.
Bossert, J. M., et al. (2012). Role of projections from ventral medial prefrontal cortex to nucleus accumbens shell in context-induced reinstatement of heroin seeking. *The Journal of Neuroscience*, *32*, 4982–4991.
Brodmann, K. (1909). *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. Barth.
Brown, S., & Sharpey-Schafer, E. A., III. (1888). An investigation into the function of the occipital and temporal lobes of the monkey's brain. *Proceedings of the Royal Society of London*, *43*, 276.
Brozoski, T. J., Brown, R. M., Rosvold, H. E., & Goldman, P. S. (1979). Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science*, *205*, 929–932.
Burgos-Robles, A., et al. (2017). Amygdala inputs to prefrontal cortex guide behavior amid conflicting cues of reward and punishment. *Nature Neuroscience*, *20*, 824–835.
Cacioppo, J. T., & Cacioppo, S. (2018). The growing problem of loneliness. *The Lancet*, *391*, 426.
Calhoon, G. G., & Tye, K. M. (2015). Resolving the neural circuits of anxiety. *Nature Neuroscience*, *18*, 1394–1404.
Calhoon, G. G., et al. (2018). Acute food deprivation rapidly modifies valence-coding microcircuits in the amygdala. *bioRxiv*, 285189. https://doi.org/10.1101/285189.
Callicott, J. H., et al. (2003). Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *The American Journal of Psychiatry*, *160*, 709–719.
Cameron, C. M., Murugan, M., Choi, J. Y., Engel, E. A., & Witten, I. B. (2019). Increased cocaine motivation is associated with degraded spatial and temporal representations in IL-NAc neurons. *Neuron*, *103*, 80. 91.e7.

Capriles, N., Rodaros, D., Sorge, R. E., & Stewart, J. (2003). A role for the prefrontal cortex in stress- and cocaine-induced reinstatement of cocaine seeking in rats. *Psychopharmacology*, *168*(66–74).
Carmichael, S. T., & Price, J. L. (1994). Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. *Journal of Comparative Neurology*, *346*, 366–402.
Carr, D. B., & Sesack, S. R. (2000a). Projections from the rat prefrontal cortex to the ventral tegmental area: Target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. *The Journal of Neuroscience*, *20*, 3864–3873.
Carr, D. B., & Sesack, S. R. (2000b). GABA-containing neurons in the rat ventral tegmental area project to the prefrontal cortex. *Synapse*, *38*, 114–123.
Castro, D. C., & Berridge, K. C. (2014). Opioid hedonic hotspot in nucleus accumbens shell: Mu, delta, and kappa maps for enhancement of sweetness "liking" and "wanting". *The Journal of Neuroscience*, *34*, 4239–4250.
Challis, C., Beck, S. G., & Berton, O. (2014). Optogenetic modulation of descending prefrontocortical inputs to the dorsal raphe bidirectionally bias socioaffective choices after social defeat. *Frontiers in Behavioral Neuroscience*, *8*, 43.
Chaudhri, N., Sahuque, L. L., & Janak, P. H. (2008). Context-induced relapse of conditioned behavioral responding to ethanol cues in rats. *Biological Psychiatry*, *64*, 203–210.
Chaudhury, D., et al. (2013). Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature*, *493*, 532–536.
Chen, Z.-Y., et al. (2006). Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science*, *314*, 140–143.
Chen, B. T., et al. (2013). Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. *Nature*, *496*, 359–362.
Ciocchi, S., et al. (2010). Encoding of conditioned fear in central amygdala inhibitory circuits. *Nature*, *468*, 277–282.
Clark, L., et al. (2008). Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. *Brain*, *131*, 1311–1322.
Clem, R. L., & Huganir, R. L. (2010). Calcium-permeable AMPA receptor dynamics mediate fear memory erasure. *Science*, *330*, 1108–1112.
Coimbra, B., et al. (2019). Role of laterodorsal tegmentum projections to nucleus accumbens in reward-related behaviors. *Nature Communications*, *10*, 4138.
Courtney, A. L., & Meyer, M. L. (2020). Self-other representation in the social brain reflects social connection. *The Journal of Neuroscience*, *40*, 5616–5627.
Davis, M., & Whalen, P. J. (2001). The amygdala: Vigilance and emotion. *Molecular Psychiatry*, *6*, 13–34.
Day, J. J., & Carelli, R. M. (2007). The nucleus accumbens and pavlovian reward learning. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *13*, 148–159.
Day, J. J., Roitman, M. F., Wightman, R. M., & Carelli, R. M. (2007). Associative learning mediates dynamic shifts in dopamine signaling in the nucleus accumbens. *Nature Neuroscience*, *10*, 1020–1028.
Dias, R., Robbins, T. W., & Roberts, A. C. (1996). Dissociation in prefrontal cortex of affective and attentional shifts. *Nature*, *380*, 69–72.
Dong, Y., Taylor, J. R., Wolf, M. E., & Shaham, Y. (2017). Circuit and synaptic plasticity mechanisms of drug relapse. *The Journal of Neuroscience*, *37*, 10867–10876.
Donoghue, J. P., & Wise, S. P. (1982). The motor cortex of the rat: Cytoarchitecture and microstimulation mapping. *Journal of Comparative Neurology*, *212*, 76–88.
Dulka, B. N., et al. (2020). Chemogenetic activation of an infralimbic cortex to basolateral amygdala projection promotes resistance to acute social defeat stress. *Scientific Reports*, *10*, 6884.

Duman, R. S., Sanacora, G., & Krystal, J. H. (2019). Altered connectivity in depression: Gaba and glutamate neurotransmitter deficits and reversal by novel treatments. *Neuron*, *102*, 75–90.
Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, *15*, 85–93.
Euston, D. R., Gruber, A. J., & McNaughton, B. L. (2012). The role of medial prefrontal cortex in memory and decision making. *Neuron*, *76*, 1057–1070.
Fanselow, M. S., & Dong, H.-W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*, *65*, 7–19.
Fanselow, M. S., & LeDoux, J. E. (1999). Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala. *Neuron*, *23*, 229–232.
Felix-Ortiz, A. C., Burgos-Robles, A., Bhagat, N. D., Leppla, C. A., & Tye, K. M. (2016). Bidirectional modulation of anxiety-related and social behaviors by amygdala projections to the medial prefrontal cortex. *Neuroscience*, *321*, 197–209.
Ferenczi, E. A., et al. (2016). Prefrontal cortical regulation of brainwide circuit dynamics and reward-related behavior. *Science*, *351*, aac9698.
File, S., & Animal, E. (1985). Models for predicting clinical efficacy of anxiolytic drugs: Social behaviour. *Neuropsychobiology*, *13*, 55–62.
Fiorino, D. F., & Phillips, A. G. (1999). Facilitation of sexual behavior and enhanced dopamine efflux in the nucleus accumbens of male rats afterd-amphetamine-induced behavioral sensitization. *The Journal of Neuroscience*, *19*, 456–463.
Floden, D., Alexander, M. P., Kubu, C. S., Katz, D., & Stuss, D. T. (2008). Impulsivity and risk-taking behavior in focal frontal lobe lesions. *Neuropsychologia*, *46*, 213–223.
Forbes, C. E., & Grafman, J. (2010). The role of the human prefrontal cortex in social cognition and moral judgment. *Annual Review of Neuroscience*, *33*, 299–324.
Fox, H. C., Bergquist, K. L., Hong, K.-I., & Sinha, R. (2007). Stress-induced and alcohol cue-induced craving in recently abstinent alcohol-dependent individuals. *Alcoholism, Clinical and Experimental Research*, *31*, 395–403.
Franklin, T. R., et al. (2002). Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biological Psychiatry*, *51*, 134–142.
Franklin, T. B., et al. (2017). Prefrontal cortical control of a brainstem social behavior circuit. *Nature Neuroscience*, *20*, 260–270.
Friedman, A., et al. (2015). A corticostriatal path targeting striosomes controls decision-making under conflict. *Cell*, *161*, 1320–1333.
Fuchs, R. A., et al. (2005). The role of the dorsomedial prefrontal cortex, basolateral amygdala, and dorsal hippocampus in contextual reinstatement of cocaine seeking in rats. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *30*, 296–309.
Fusi, S., Miller, E. K., & Rigotti, M. (2016). Why neurons mix: High dimensionality for higher cognition. *Current Opinion in Neurobiology*, *37*, 66–74.
Gabbott, P. L. A., Warner, T. A., Jays, P. R. L., Salway, P., & Busby, S. J. (2005). Prefrontal cortex in the rat: Projections to subcortical autonomic, motor, and limbic centers. *Journal of Comparative Neurology*, *492*, 145–177.
Galynker, I. I., et al. (1998). Hypofrontality and negative symptoms in major depressive disorder. *The Journal of Nuclear Medicine: The Official Journal of the Society of Nuclear Medicine*, *39*, 608–612.
Gawin, F. H., & Kleber, H. D. (1988). Evolving conceptualizations of cocaine dependence. *The Yale Journal of Biology and Medicine*, *61*, 123–136.
George, O., & Koob, G. F. (2013). Control of craving by the prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 4165–4166.
Goldman-Rakic, P. S. (1996). Regional and cellular fractionation of working memory. *Proceedings of the National Academy of Sciences*, *93*, 13473–13480.

Goldstein, R. Z., et al. (2007). Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? *The American Journal of Psychiatry*, *164*, 43–51.
Grabenhorst, F., & Rolls, E. T. (2011). Value, pleasure and choice in the ventral prefrontal cortex. *Trends in Cognitive Sciences*, *15*, 56–67.
Grace, A. A., Floresco, S. B., Goto, Y., & Lodge, D. J. (2007). Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. *Trends in Neurosciences*, *30*, 220–227.
Grafman, J., et al. (1996). Frontal lobe injuries, violence, and aggression: A report of the Vietnam Head Injury Study. *Neurology*, *46*, 1231–1238.
Grigson, P. S., & Twining, R. C. (2002). Cocaine-induced suppression of saccharin intake: A model of drug-induced devaluation of natural rewards. *Behavioral Neuroscience*, *116*, 321–333.
Grimm, J. W., Hope, B. T., Wise, R. A., & Shaham, Y. (2001). Incubation of cocaine craving after withdrawal. *Nature*, *412*, 141–142.
Grunfeld, I. S., & Likhtik, E. (2018). Mixed selectivity encoding and action selection in the prefrontal cortex during threat assessment. *Current Opinion in Neurobiology*, *49*, 108–115.
Gunaydin, L. A., et al. (2014). Natural neural projection dynamics underlying social behavior. *Cell*, *157*, 1535–1551.
Halladay, L. R., et al. (2020). Prefrontal regulation of punished ethanol self-administration. *Biological Psychiatry*, *87*, 967–978.
Hamani, C., et al. (2011). The subcallosal cingulate gyrus in the context of major depression. *Biological Psychiatry*, *69*, 301–308.
Han, J.-H., et al. (2007). Neuronal competition and selection during memory formation. *Science*, *316*, 457–460.
Han, J.-H., et al. (2009). Selective erasure of a fear memory. *Science*, *323*, 1492–1496.
Harlow, J. M. (1868). Recovery from passage of an iron bar through the head. B. Mass. *Medicine and Society*, *2*, 3–20.
Harlow, J. M. (1993). Recovery from the passage of an iron bar through the head. *History of Psychiatry*, *4*, 274–281.
Harvey, P.-O., Pruessner, J., Czechowska, Y., & Lepage, M. (2007). Individual differences in trait anhedonia: A structural and functional magnetic resonance imaging study in non-clinical subjects. *Molecular Psychiatry*, *12*(703), 767–775.
Heidbreder, C. A., & Groenewegen, H. J. (2003). The medial prefrontal cortex in the rat: Evidence for a dorso-ventral distinction based upon functional and anatomical characteristics. *Neuroscience and Biobehavioral Reviews*, *27*, 555–579.
Hitora-Imamura, N., et al. (2015). Prefrontal dopamine regulates fear reinstatement through the downregulation of extinction circuits. *eLife*, *4*, e08274.
Hornak, J., Rolls, E. T., & Wade, D. (1996). Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia*, *34*, 247–261.
Hornak, J., et al. (2003). Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain: A Journal of Neurology*, *126*, 1691–1712.
Huang, W.-C., Zucca, A., Levy, J., & Page, D. T. (2020). Social behavior is modulated by valence-encoding mPFC-amygdala sub-circuitry. *Cell Reports*, *32*, 107899.
Hunt, P. R., & Aggleton, J. P. (1991). Medial dorsal thalamic lesions and working memory in the rat. *Behavioral and Neural Biology*, *55*, 227–246.
Hyman, S. E. (2005). Addiction: A disease of learning and memory. *The American Journal of Psychiatry*, *162*, 1414–1422.
James, M. H., McGlinchey, E. M., Vattikonda, A., Mahler, S. V., & 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. *The International Journal of Neuropsychopharmacology*, *21*, 89–94.

Janak, P. H., & Tye, K. M. (2015). From circuits to behaviour in the amygdala. *Nature*, *517*, 284–292.
Jankowski, M. P., & Sesack, S. R. (2004). Prefrontal cortical projections to the rat dorsal raphe nucleus: Ultrastructural features and associations with serotonin and gamma-aminobutyric acid neurons. *Journal of Comparative Neurology*, *468*, 518–529.
Jasinska, A. J., Stein, E. A., Kaiser, J., Naumer, M. J., & Yalachkov, Y. (2014). Factors modulating neural reactivity to drug cues in addiction: A survey of human neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *38*, 1–16.
Jennings, J. H., et al. (2019). Interacting neural ensembles in orbitofrontal cortex for social and feeding behaviour. *Nature*, *565*, 645–649.
Johansen-Berg, H., et al. (2008). Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cerebral Cortex (New York, N.Y.)*, *1991*(18), 1374–1383.
Johnston, W. J., Palmer, S. E., & Freedman, D. J. (2020). Nonlinear mixed selectivity supports reliable neural computation. *PLoS Computational Biology*, *16*, e1007544.
Kalivas, P. W., Volkow, N., & Seamans, J. (2005). Unmanageable motivation in addiction: A pathology in prefrontal-accumbens glutamate transmission. *Neuron*, *45*, 647–650.
Kamii, H., et al. (2015). Intrinsic membrane plasticity via increased persistent sodium conductance of cholinergic neurons in the rat laterodorsal tegmental nucleus contributes to cocaine-induced addictive behavior. *The European Journal of Neuroscience*, *41*, 1126–1138.
Kang, H. J., et al. (2012). Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. *Nature Medicine*, *18*, 1413–1417.
Keedwell, P. A., Andrew, C., Williams, S. C. R., Brammer, M. J., & Phillips, M. L. (2005). The neural correlates of anhedonia in major depressive disorder. *Biological Psychiatry*, *58*, 843–853.
Kennerley, S. W., Dahmubed, A. F., Lara, A. H., & Wallis, J. D. (2009). Neurons in the frontal lobe encode the value of multiple decision variables. *Journal of Cognitive Neuroscience*, *21*, 1162–1178.
Kennerley, S. W., & Wallis, J. D. (2009). Encoding of reward and space during a working memory task in the orbitofrontal cortex and anterior cingulate sulcus. *Journal of Neurophysiology*, *102*, 3352–3364.
Kennerley, S. W., & Walton, M. E. (2011). Decision making and reward in frontal cortex. *Behavioral Neuroscience*, *125*, 297–317.
Kerstetter, K. A., et al. (2016). Corticostriatal afferents modulate responsiveness to psychostimulant drugs and drug-associated stimuli. *Neuropsychopharmacology*, *41*, 1128–1137.
Kim, S., Hwang, J., & Lee, D. (2008). Prefrontal coding of temporally discounted values during inter-temporal choice. *Neuron*, *59*, 161–172.
Kim, C. K., et al. (2017). Molecular and circuit-dynamical identification of top-down neural mechanisms for restraint of reward seeking. *Cell*, *170*, 1013. 1027.e14.
Kingsbury, L., et al. (2019). Correlated neural activity and encoding of behavior across brains of socially interacting animals. *Cell*, *178*, 429. 446.e16.
Klavir, O., Genud-Gabai, R., & Paz, R. (2013). Functional connectivity between amygdala and cingulate cortex for adaptive aversive learning. *Neuron*, *80*, 1290–1300.
Klüver, H., & Bucy, P. C. (1937). 'Psychic blindness' and other symptoms following bilateral temporal lobectomy in Rhesus monkeys. *The American Journal of Physiology*, *119*, 352–353.
Koob, G. F., & Le Moal, M. (2008). Neurobiological mechanisms for opponent motivational processes in addiction. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *363*, 3113–3123.
Kunwar, P. S., et al. (2015). Ventromedial hypothalamic neurons control a defensive emotion state. *eLife*, *4*, e06633.

Kurosawa, R., Taoka, N., Shinohara, F., Minami, M., & Kaneda, K. (2013). Cocaine exposure enhances excitatory synaptic drive to cholinergic neurons in the laterodorsal tegmental nucleus. *The European Journal of Neuroscience*, *38*, 3027–3035.

Kutlu, M. G., & Gould, T. J. (2016). Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: Contributions to development and maintenance of addiction. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *23*, 515–533.

Kyriazi, P., Headley, D. B., & Pare, D. (2018). Multi-dimensional coding by basolateral amygdala neurons. *Neuron*. https://doi.org/10.1016/j.neuron.2018.07.036.

Lammel, S., Ion, D. I., Roeper, J., & Malenka, R. C. (2011). Projection-specific modulation of dopamine neuron synapses by aversive and rewarding stimuli. *Neuron*, *70*, 855–862.

Lammel, S., Tye, K. M., & Warden, M. R. (2013). Progress in understanding mood disorders: Optogenetic dissection of neural circuits. *Genes, Brain, and Behavior*. https://doi.org/10.1111/gbb.12049.

Lammel, S., et al. (2012). Input-specific control of reward and aversion in the ventral tegmental area. *Nature*, *491*, 212–217.

Lang, P. J. (1995). The emotion probe: Studies of motivation and attention. *The American Psychologist*, *50*, 372–385.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychological Review*, *97*, 377–395.

Laubach, M., Amarante, L. M., Swanson, K., & White, S. R. (2018). What, if anything, is rodent prefrontal cortex? *eNeuro*, *5*.

LeDoux, J. E. (1996). *The emotional brain: The mysterious underpinnings of emotional life* (p. 384). Simon & Schuster.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, *23*, 155–184.

Lee, T. G., & D'Esposito, M. (2012). The dynamic nature of top-down signals originating from prefrontal cortex: A combined fMRI–TMS study. *The Journal of Neuroscience*, *32*, 15458–15466.

Lee, J. S., Jung, S., Park, I. H., & Kim, J.-J. (2015). Neural basis of anhedonia and amotivation in patients with schizophrenia: The role of reward system. *Current Neuropharmacology*, *13*, 750–759.

Levy, D. R., et al. (2019). Dynamics of social representation in the mouse prefrontal cortex. *Nature Neuroscience*, *22*, 2013–2022.

Li, A., et al. (2019). Role of BDNF in the development of an OFC-amygdala circuit regulating sociability in mouse and human. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-019-0422-4.

Lin, D., et al. (2011). Functional identification of an aggression locus in the mouse hypothalamus. *Nature*, *470*, 221–226.

Litt, M. D., & Cooney, N. L. (1999). Inducing craving for alcohol in the laboratory. *Alcohol Research & Health: The Journal of the National Institute on Alcohol Abuse and Alcoholism*, *23*, 174–178.

Lo, L., et al. (2019). Connectional architecture of a mouse hypothalamic circuit node controlling social behavior. *Proceedings of the National Academy of Sciences*, *116*, 7503–7512.

Ma, T., Cheng, Y., Hellard, E., Wang, X., Lu, J., Gao, X., et al. (2018). Bidirectional and long-lasting control of alcohol-seeking behavior by corticostriatal LTP and LTD. *Nature Neuroscience*, *21*(3), 373–383. https://doi.org/10.1038/s41593-018-0081-9.

Ma, Y.-Y., et al. (2014). Bi-directional modulation of incubation of cocaine craving by silent synapse-based remodeling of prefrontal cortex to accumbens projections. *Neuron*, *83*, 1453–1467.

Machens, C. K., Romo, R., & Brody, C. D. (2010). Functional, but not anatomical, separation of "what" and "when" in prefrontal cortex. *The Journal of Neuroscience*, *30*, 350–360.

Maier, S. (2015). Behavioral control blunts reactions to contemporaneous and future adverse events: Medial prefrontal cortex plasticity and a corticostriatal network. *Neurobiol. Stress*. https://doi.org/10.1016/j.ynstr.2014.09.003.
Mante, V., Sussillo, D., Shenoy, K. V., & Newsome, W. T. (2013). Context-dependent computation by recurrent dynamics in prefrontal cortex. *Nature*, *503*, 78–84.
Mantz, J., Thierry, A. M., & Glowinski, J. (1989). Effect of noxious tail pinch on the discharge rate of mesocortical and mesolimbic dopamine neurons: Selective activation of the mesocortical system. *Brain Research*, *476*, 377–381.
Marek, R., et al. (2018). Hippocampus-driven feed-forward inhibition of the prefrontal cortex mediates relapse of extinguished fear. *Nature Neuroscience*, *21*, 384–392.
Maren, S. (2001). Neurobiology of pavlovian fear conditioning. *Annual Review of Neuroscience*, *24*, 897–931.
Maren, S., & Quirk, G. J. (2004). Neuronal signalling of fear memory. *Nature Reviews. Neuroscience*, *5*, 844–852.
Matsumoto, M., & Hikosaka, O. (2007). Lateral habenula as a source of negative reward signals in dopamine neurons. *Nature*, *447*, 1111–1115.
Matsumoto, M., & Hikosaka, O. (2009). Representation of negative motivational value in the primate lateral habenula. *Nature Neuroscience*, *12*, 77–84.
Matthews, G. A., & Tye, K. M. (2019). Neural mechanisms of social homeostasis. *Annals. New York Academy of Sciences*, *1457*, 5–25.
Mayberg, H. S., et al. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron*, *45*, 651–660.
McFarland, K., Davidge, S. B., Lapish, C. C., & Kalivas, P. W. (2004). Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. *The Journal of Neuroscience*, *24*, 1551–1560.
McGinnis, M. M., Parrish, B. C., Chappell, A. M., Alexander, N. J., & McCool, B. A. (2020). Chronic ethanol differentially modulates glutamate release from dorsal and ventral prefrontal cortical inputs onto rat basolateral amygdala principal neurons. *eNeuro*, 7.
McGlinchey, E. M., James, M. H., Mahler, S. V., 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. *The Journal of Neuroscience*, *36*, 8700–8711.
Méndez-Bértolo, C., et al. (2016). A fast pathway for fear in human amygdala. *Nature Neuroscience*, *19*, 1041–1049.
Miller, E. K. (1999). The prefrontal cortex: Complex neural properties for complex behavior. *Neuron*, *22*, 15–17.
Miller, E. K., & Buschman, T. J. (2013). Cortical circuits for the control of attention. *Current Opinion in Neurobiology*, *23*, 216–222.
Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202.
Moniz, E. (1937). Prefrontal leucotomy in the treatment of mental disorders. *The American Journal of Psychiatry*, *93*, 1379–1385.
Moorman, D. E., James, M. H., McGlinchey, E. M., & Aston-Jones, G. (2015). Differential roles of medial prefrontal subregions in the regulation of drug seeking. *Brain Research*, *1628*, 130–146.
Moreines, J. L., Owrutsky, Z. L., & Grace, A. A. (2017). Involvement of infralimbic prefrontal cortex but not lateral habenula in dopamine attenuation after chronic mild stress. *Neuropsychopharmacology*, *42*, 904–913.
Muir, J., Lopez, J., & Bagot, R. C. (2019). Wiring the depressed brain: Optogenetic and chemogenetic circuit interrogation in animal models of depression. *Neuropsychopharmacology*, *44*, 1013–1026.

Murrough, J. W., Abdallah, C. G., & Mathew, S. J. (2017). Targeting glutamate signalling in depression: Progress and prospects. *Nature Reviews. Drug Discovery*, *16*, 472–486.
Murugan, M., et al. (2017). Combined social and spatial coding in a descending projection from the prefrontal cortex. *Cell*, *171*, 1663. 1677.e16.
Namburi, P., et al. (2015). A circuit mechanism for differentiating positive and negative associations. *Nature*, *520*, 675–678.
Naya, Y., Chen, H., Yang, C., & Suzuki, W. A. (2017). Contributions of primate prefrontal cortex and medial temporal lobe to temporal-order memory. *Proceedings of the National Academy of Sciences*, *114*, 13555–13560.
Narita, M., et al. (2010). Implication of dopaminergic projection from the ventral tegmental area to the anterior cingulate cortex in μ-opioid-induced place preference. *Addiction Biology*, *14*, 434–447.
Nelson, A. C., et al. (2019). Molecular and circuit architecture of social hierarchy. *bioRxiv*, 838664.
Nocjar, C., & Panksepp, J. (2002). Chronic intermittent amphetamine pretreatment enhances future appetitive behavior for drug- and natural-reward: Interaction with environmental variables. *Behavioural Brain Research*, *128*, 189–203.
Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. E. (2002). Rethinking feelings: An FMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, *14*, 1215–1229.
Ochsner, K. N., et al. (2009). Bottom-up and top-down processes in emotion generation. *Psychological Science*, *20*, 1322–1331.
Ongür, D., Ferry, A. T., & Price, J. L. (2003). Architectonic subdivision of the human orbital and medial prefrontal cortex. *Journal of Comparative Neurology*, *460*, 425–449.
Ongür, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb. Cortex N. Y. N*, *1991*(10), 206–219.
Otis, J. M., et al. (2017). Prefrontal cortex output circuits guide reward seeking through divergent cue encoding. *Nature*, *543*, 103–107.
Papez, J. W. (1937). A proposed mechanism of emotion. *Archives of Neurology and Psychiatry*, *38*, 725–743.
Parnaudeau, S., et al. (2013). Inhibition of mediodorsal thalamus disrupts thalamofrontal connectivity and cognition. *Neuron*, *77*, 1151–1162.
Parthasarathy, A., et al. (2017). Mixed selectivity morphs population codes in prefrontal cortex. *Nature Neuroscience*, *20*, 1770–1779.
Pascoli, V., et al. (2014). Contrasting forms of cocaine-evoked plasticity control components of relapse. *Nature*, *509*, 459–464.
Passingham, R. E., & Wise, S. P. (2014). *The neurobiology of the prefrontal cortex: Anatomy, evolution, and the origin of insight*. xxii, 399 Oxford University Press.
Paton, J. J., Belova, M. A., Morrison, S. E., & Salzman, C. D. (2006). The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature*, *439*, 865–870.
Pennington, B. F., & Bennetto, L. (1993). Main effects or transactions in the neuropsychology of conduct disorder? Commentary on "The neuropsychology of conduct disorder". *Development and Psychopathology*, *5*, 153–164.
Perry, C. J., Zbukvic, I., Kim, J. H., & Lawrence, A. J. (2014). Role of cues and contexts on drug-seeking behaviour. *British Journal of Pharmacology*, *171*, 4636–4672.
Peters, J., Kalivas, P. W., & Quirk, G. J. (2009). Extinction circuits for fear and addiction overlap in prefrontal cortex. *Learning & Memory*, *16*, 279–288.
Petrides, M. (1995). Functional organization of the human frontal cortex for mnemonic processing. Evidence from neuroimaging studies. *Annals of the New York Academy of Sciences*, *769*, 85–96.

Peyron, C., Petit, J.-M., Rampon, C., Jouvet, M., & Luppi, P.-H. (1997). Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. *Neuroscience*, *82*, 443–468.
Phelps, E. A., & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron*, *48*, 175–187.
Pizzagalli, D., & Depression, A. (2014). Stress, and anhedonia: Toward a synthesis and integrated model. *Annual Review of Clinical Psychology*, *10*, 393–423.
Place, R., Farovik, A., Brockmann, M., & Eichenbaum, H. (2016). Bidirectional prefrontal-hippocampal interactions support context-guided memory. *Nature Neuroscience*, *19*, 992–994.
Popescu, A. T., Zhou, M. R., & Poo, M.-M. (2016). Phasic dopamine release in the medial prefrontal cortex enhances stimulus discrimination. *Proceedings of the National Academy of Sciences of the United States of America*, *113*, E3169–E3176.
Powell, N. J., & Redish, A. D. (2014). Complex neural codes in rat prelimbic cortex are stable across days on a spatial decision task. *Frontiers in Behavioral Neuroscience*, *8*.
Quirk, G. J., & Beer, J. S. (2006). Prefrontal involvement in the regulation of emotion: Convergence of rat and human studies. *Current Opinion in Neurobiology*, *16*, 723–727.
Ramirez-Cardenas, A., & Viswanathan, P. (2016). The role of prefrontal mixed selectivity in cognitive control. *The Journal of Neuroscience*, *36*, 9013–9015.
Randall, P. A., McElligott, Z. A., & Besheer, J. (2020). Role of mPFC and nucleus accumbens circuitry in modulation of a nicotine plus alcohol compound drug state. *Addiction Biology*, *25*, e12782.
Reid, M. S., Flammino, F., Starosta, A., Palamar, J., & Franck, J. (2006). Physiological and subjective responding to alcohol cue exposure in alcoholics and control subjects: Evidence for appetitive responding. *Journal of Neural Transmission (Vienna, Austria)*, *1996*(113), 1519–1535.
Reijmers, L. G., Perkins, B. L., Matsuo, N., & Mayford, M. (2007). Localization of a stable neural correlate of associative memory. *Science*, *317*, 1230–1233.
Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science*, *306*, 443–447.
Riga, D., et al. (2014). Optogenetic dissection of medial prefrontal cortex circuitry. *Frontiers in Systems Neuroscience*, *8*.
Rigotti, M., et al. (2013). The importance of mixed selectivity in complex cognitive tasks. *Nature*, *497*, 585–590.
Rogers, J. L., & See, R. E. (2007). Selective inactivation of the ventral hippocampus attenuates cue-induced and cocaine-primed reinstatement of drug-seeking in rats. *Neurobiology of Learning and Memory*, *87*, 688–692.
Rolls, E. T., & Grabenhorst, F. (2008). The orbitofrontal cortex and beyond: From affect to decision-making. *Progress in Neurobiology*, *86*, 216–244.
Rumpel, S., LeDoux, J., Zador, A., & Malinow, R. (2005). Postsynaptic receptor trafficking underlying a form of associative learning. *Science*, *308*, 83–88.
Russell, J. A. (1980). A circumplex model of affect. *Journal of Personality and Social Psychology*, *39*, 1161–1178.
Sawaguchi, T., & Goldman-Rakic, P. S. (1991). D1 dopamine receptors in prefrontal cortex: Involvement in working memory. *Science*, *251*, 947–950.
Schlaepfer, T. E., et al. (2008). Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology*, *33*, 368–377.
Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science*, *275*, 1593–1599.
Seger, C. A., Stone, M., & Keenan, J. P. (2004). Cortical Activations during judgments about the self and an other person. *Neuropsychologia*, *42*, 1168–1177.
Seif, T., et al. (2013). Cortical activation of accumbens hyperpolarization-active NMDARs mediates aversion-resistant alcohol intake. *Nature Neuroscience*, *16*, 1094–1100.
Semendeferi, K., Damasio, H., Frank, R., & Van Hoesen, G. W. (1997). The evolution of the frontal lobes: A volumetric analysis based on three-dimensional reconstructions of magnetic resonance scans of human and ape brains. *Journal of Human Evolution*, *32*, 375–388.

Semendeferi, K., Lu, A., Schenker, N., & Damasio, H. (2002). Humans and great apes share a large frontal cortex. *Nature Neuroscience*, *5*, 272–276.
Seo, D., et al. (2013). Disrupted ventromedial prefrontal function, alcohol craving, and subsequent relapse risk. *JAMA Psychiatry Chic. Ill*, *70*, 727–739.
Seo, C., et al. (2019). Intense threat switches dorsal raphe serotonin neurons to a paradoxical operational mode. *Science*, *363*, 538–542.
Sesack, S. R., Deutch, A. Y., Roth, R. H., & Bunney, B. S. (1989). Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: An anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. *Journal of Comparative Neurology*, *290*, 213–242.
Sf, M., & Lr, W. (2005). Stressor controllability and learned helplessness: The roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. *Neuroscience and Biobehavioral Reviews*, *29*. https://pubmed.ncbi.nlm.nih.gov/15893820/.
Shabel, S. J., & Janak, P. H. (2009). Substantial similarity in amygdala neuronal activity during conditioned appetitive and aversive emotional arousal. *Proceedings of the National Academy of Sciences*, *106*, 15031–15036.
Siciliano, C. A., et al. (2019). A cortical-brainstem circuit predicts and governs compulsive alcohol drinking. *Science*, *366*, 1008–1012.
Solomon, R. L. (1980). The opponent-process theory of acquired motivation: The costs of pleasure and the benefits of pain. *The American Psychologist*, *35*, 691–712.
Song, J., et al. (2019). Crucial role of feedback signals from prelimbic cortex to basolateral amygdala in the retrieval of morphine withdrawal memory. *Science Advances*, *5*, eaat3210.
Sotres-Bayon, F., & Quirk, G. J. (2010). Prefrontal control of fear: More than just extinction. *Current Opinion in Neurobiology*, *20*, 231–235.
Spealman, R. D., et al. (2004). Triggers of relapse: Nonhuman primate models of reinstated cocaine seeking. *Nebraska Symposium on Motivation*, *50*, 57–84.
Stefanik, M. T., & Kalivas, P. W. (2013). Optogenetic dissection of basolateral amygdala projections during cue-induced reinstatement of cocaine seeking. *Frontiers in Behavioral Neuroscience*, *7*.
Stefanik, M. T., Kupchik, Y. M., & Kalivas, P. W. (2016). Optogenetic inhibition of cortical afferents in the nucleus accumbens simultaneously prevents cue-induced transient synaptic potentiation and cocaine-seeking behavior. *Brain Structure & Function*, *221*, 1681–1689.
Stefanik, M. T., et al. (2013). Optogenetic inhibition of cocaine seeking in rats. *Addiction Biology*, *18*, 50–53.
Sul, J. H., Kim, H., Huh, N., Lee, D., & Jung, M. W. (2010). Distinct roles of rodent orbitofrontal and medial prefrontal cortex in decision making. *Neuron*, *66*, 449–460.
Takahashi, Y. K., et al. (2009). The orbitofrontal cortex and ventral tegmental area are necessary for learning from unexpected outcomes. *Neuron*, *62*, 269–280.
Tamietto, M., & de Gelder, B. (2010). Neural bases of the non-conscious perception of emotional signals. *Nature Reviews. Neuroscience*, *11*, 697–709.
Taylor, J. R., & Horger, B. A. (1999). Enhanced responding for conditioned reward produced by intra-accumbens amphetamine is potentiated after cocaine sensitization. *Psychopharmacology*, *142*(31–40).
Tierney, A., & Egas, J. (2000). Moniz and the origins of psychosurgery: A review commemorating the 50th anniversary of Moniz's Nobel Prize. *Journal of the History of the Neurosciences*, *9*, 22–36.
Tsuchida, A., & Fellows, L. K. (2012). Are You Upset? Distinct roles for orbitofrontal and lateral prefrontal cortex in detecting and distinguishing facial expressions of emotion. *Cerebral Cortex*, *22*, 2904–2912.
Tsuda, B., Tye, K. M., Siegelmann, H. T., & Sejnowski, T. J. (2020). A modeling framework for adaptive lifelong learning with transfer and savings through gating in the prefrontal cortex. *bioRxiv*. https://doi.org/10.1101/2020.03.11.984757. 2020.03.11.984757.
Tye, K. M. (2018). Neural circuit motifs in valence processing. *Neuron*, *100*, 436–452.
Tye, K. M., et al. (2011). Amygdala circuitry mediating reversible and bidirectional control of anxiety. *Nature*, *471*, 358–362.

Tye, K. M., et al. (2013). Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature*, *493*, 537–541.
Van den Oever, M. C., Spijker, S., Smit, A. B., & De Vries, T. J. (2010). Prefrontal cortex plasticity mechanisms in drug seeking and relapse. *Neuroscience and Biobehavioral Reviews*, *35*, 276–284.
Vander Weele, C. M., Siciliano, C. A., & Tye, K. M. (2018). Dopamine tunes prefrontal outputs to orchestrate aversive processing. *Brain Research*. https://doi.org/10.1016/j.brainres.2018.11.044.
Vander Weele, C. M., et al. (2018). Dopamine enhances signal-to-noise ratio in cortical-brainstem encoding of aversive stimuli. *Nature*, *563*, 397–401.
Vertes, R. P. (2004). Differential projections of the infralimbic and prelimbic cortex in the rat. *Synapse*, *51*, 32–58.
Volkow, N. D., & Fowler, J. S. (2000). Addiction, a disease of compulsion and drive: Involvement of the orbitofrontal cortex. *Cerebral Cortex (New York, N.Y.)*, *1991*(10), 318–325.
Volkow, N. D., Fowler, J. S., & Wang, G.-J. (2003). The addicted human brain: Insights from imaging studies. *The Journal of Clinical Investigation*, *111*, 1444–1451.
Volkow, N. D., et al. (1997). Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature*, *386*, 827–830.
Wallis, J., & Orbitofrontal, D. (2007). Cortex and its contribution to decision-making. *Annual Review of Neuroscience*, *30*, 31–56.
Walton, M. E., Devlin, J. T., & Rushworth, M. F. S. (2004). Interactions between decision making and performance monitoring within prefrontal cortex. *Nature Neuroscience*, *7*, 1259–1265.
Wang, Q., Jin, J., & Maren, S. (2016). Renewal of extinguished fear activates ventral hippocampal neurons projecting to the prelimbic and infralimbic cortices in rats. *Neurobiology of Learning and Memory*, *134*(Pt A), 38–43.
Wang, N., et al. (2018). Role of Glutamatergic Projections from the Ventral CA1 to Infralimbic Cortex in Context-Induced Reinstatement of Heroin Seeking. *Neuropsychopharmacology*, *43*, 1373–1384.
Wang, Y., et al. (2019). Opiate-associated contextual memory formation and retrieval are differentially modulated by dopamine D1 and D2 signaling in hippocampal-prefrontal connectivity. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.*, *44*, 334–343.
Warden, M. R., et al. (2012). A prefrontal cortex–brainstem neuronal projection that controls response to behavioural challenge. *Nature*, *492*, 428–432.
Weiskrantz, L. (1956). Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *Journal of Comparative and Physiological Psychology*, *49*, 381–391.
Wyvell, C. L., & Berridge, K. C. (2001). Incentive sensitization by previous amphetamine exposure: Increased cue-triggered 'wanting' for sucrose reward. *Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *21*, 7831–7840.
Xiao, C., et al. (2016). Cholinergic mesopontine signals govern locomotion and reward through dissociable midbrain pathways. *Neuron*, *90*, 333–347.
Yizhar, O., & Klavir, O. (2018). Reciprocal amygdala–prefrontal interactions in learning. *Current Opinion in Neurobiology*, *52*, 149–155.
Zhao, Y., et al. (2017). Memory retrieval in addiction: A role for miR-105-mediated regulation of D1 receptors in mPFC neurons projecting to the basolateral amygdala. *BMC Biology*, *15*.
Zhou, T., et al. (2017). History of winning remodels thalamo-PFC circuit to reinforce social dominance. *Science*, *357*, 162–168.
Zironi, I., Burattini, C., Aicardi, G., & Janak, P. H. (2006). Context is a trigger for relapse to alcohol. *Behavioural Brain Research*, *167*, 150–155.