Integration of value and action in medial prefrontal neural systems

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Abstract

The rodent medial prefrontal cortex (mPFC) plays a key role in regulating cognition, emotion, and behavior. mPFC neurons are activated in diverse experimental paradigms, raising the questions of whether there are specific task elements or dimensions encoded by mPFC neurons, and whether these encoded parameters are selective to neurons in particular mPFC subregions or networks. Here, we consider the role of mPFC neurons in processing appetitive and aversive cues, outcomes, and related behaviors. mPFC neurons are strongly activated in tasks probing value and outcome-associated actions, but these responses vary across experimental paradigms. Can we identify specific categories of responses (e.g., positive or negative value), or do mPFC neurons exhibit response properties that are too heterogeneous/complex to cluster into distinct conceptual groups? Based on a review of relevant studies, we consider what has been done and what needs to be further explored in order to address these questions.

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1. Rodent medial prefrontal cortex

The prefrontal cortex (PFC) plays important roles in cognition, motivation, and behavior control (Cassaday, Nelson, & Pezze, 2014; Dalley, Cardinal, & Robbins, 2004; Euston, Gruber, & McNaughton, 2012; Miller & Cohen, 2001). However, the specifics and extent of what is being encoded in PFC circuit activity remain unclear. The PFC is highly interconnected with structures throughout the brain, and the resulting integrations produce complex computations at the circuit level. Although progress has been made in characterizing these computations in the service of understanding behavioral contributions of the PFC, the boundaries and intersection points of its functional roles are still poorly defined.

Although much of the research on PFC has been performed in human and non-human primates (Laubach, Amarante, Swanson, & White, 2018; Miller & Cohen, 2001; Passingham & Wise, 2012), there is a rich history of investigating PFC function in rodents, and interest has increased in recent years (Laubach et al., 2018). Despite concerns with rodent-primate homology (Preuss, 1995; Wise, 2008), anatomical parallels can guide cross-species comparisons (Heilbronner, Rodriguez-Romaguera, Quirk, Groenewegen, & Haber, 2016; Ongur & Price, 2000). Further, it is indisputable that rodents are capable of producing complex cognitive- and emotionally-driven behaviors, at least some of which activate and are impacted by manipulation of PFC. Thus, irrespective of specific anatomical homologies, there are functional equivalences across species that warrant investigating the rodent PFC as a key component of complex behavior (Brown & Bowman, 2002; Dalley et al., 2004; Kesner & Churchwell, 2011; Seamans, Lapish, & Durstewitz, 2008; Uylings, Groenewegen, & Kolb, 2003).

Most rodent studies of PFC focus on the medial PFC (mPFC), subdividing it into prelimbic (PL) and infralimbic (IL) cortex based on location, connectivity and function. Anterior cingulate cortex (ACC) is sometimes incorporated but more often separated based on anatomical and functional grounds, and orbitofrontal cortex (OFC) is typically considered separately (Gabbott, Warner, Jays, Salway, & Busby, 2005; Heidbreder & Groenewegen, 2003; Izquierdo, 2017; van Heukelum et al., 2020; Vertes, 2006). There is also some discussion about which regions constitute PFC (Laubach et al., 2018) and a growing interest in characterizing complex functions associated with frontal regions outside of ACC/PL/IL. Areas such as secondary motor cortex, frontal orienting fields, and frontal association cortex have been probed as being part of rodent prefrontal cortex (Barthas & Kwan, 2017; Ebbesen et al., 2018; Erlich, Bialek, & Brody, 2011). Although there is fascinating work being performed to elucidate the functions of these regions, here we will focus on the PL and IL "core" of mPFC.

2. Medial prefrontal neuronal representations of value and motivation

Here, we consider mPFC neural correlates of positive and negative value and how these signals interact with motivated action. There is clearly a relationship between mPFC neural function and outcome value as shown by the studies described below. Representations of outcomes, cues predicting outcomes, and actions needed to approach or avoid outcomes, are fundamental to almost all behaviors associated with mPFC function. Underlying cognition-probing tasks is the need for a motivated action. Outcome or value signals are frequently seen in these tasks—see, for example, action and outcome encoding during behavioral flexibility testing in (Del Arco, Park, Wood, Kim, & Moghaddam, 2017). Consideration of value also allows some cross-study comparisons. Although many studies of mPFC function are siloed in specific experimental paradigms or themes, a few have probed mPFC function associated with different values, bridging across research domains to understand the diversity of mPFC encoding. Finally, understanding value representations is of translational importance with potential implications for drug and alcohol dependence, eating disorders, ADHD and other disorders of impulsivity, depression, and other psychiatric diseases. A focus on studies investigating representation of value neglects much of the diversity of neural signaling in mPFC. However, given the pervasiveness of value in almost all behaviors, consideration of mPFC function in the context of value is worthwhile in understanding fundamental properties of this complex system.

3. Negative value: Punishment, fear, and aversion

Early studies of rodent mPFC neural activity described correlates of aversive learning (Peterson, 1986), supporting even earlier studies of cat and rabbit mPFC, e.g., (Gabriel & Orona, 1982). There has since been significant interest in mPFC activity related to learning and behaviors associated with negative outcomes (Gilmartin, Balderston, & Helmstetter, 2014; Giustino & Maren, 2015; Grunfeld & Likhtik, 2018; Maren & Quirk, 2004;

Rozeske & Herry, 2018; Sotres-Bayon & Quirk, 2010). This has been driven by at least two goals—first to understand neuronal representation of negatively-valenced emotions and outcomes, and second to understand neuronal mechanisms underlying learning and memory, as learning in Pavlovian fear conditioning paradigms is rapid and robust. This intersection between value/emotion representation and learning underscores the point that experimental paradigms incorporate multiple dimensions (outcomes, behaviors, learning), even when the primary research goal is focused on understanding one particular phenomenon.

Potentially reflecting these multiple dimensions, early studies of mPFC activity during fear conditioning identified that many neurons recorded responded to a shock-predicting cue, but that neuronal responses were diverse, lasting different durations and exhibiting both excitatory and inhibitory properties (Baeg et al., 2001; Garcia, Vouimba, Baudry, & Thompson, 1999; Peterson, 1986). Studies have repeatedly reported neuronal responses to aversive cues and outcomes, typically during fear conditioning involving shock stimuli, though studies have also reported mPFC neuronal responses to primary aversive stimuli (Jezzini, Mazzucato, La Camera, & Fontanini, 2013; Zhang, Tomida, Katayama, & Kawakami, 2004).

There is a relatively dichotomous role for PL vs IL in fear conditioning and expression vs extinction. PL neurons are generally activated by aversive outcomes and cues that predict them, and IL neurons are generally inhibited by aversive outcome-predicting cues and increase firing during extinction of fear-conditioned cues (Burgos-Robles, Vidal-Gonzalez, & Quirk, 2009; Gilmartin & McEchron, 2005; Giustino, Fitzgerald, Ressler, & Maren, 2019; Milad & Quirk, 2002; Sotres-Bayon, Sierra-Mercado, Pardilla-Delgado, & Quirk, 2012). These data support studies using PL or IL neuron manipulation, in which similar dichotomies have been observed (Courtin, Bienvenu, Einarsson, & Herry, 2013; Gilmartin et al., 2014; Giustino & Maren, 2015; Sotres-Bayon & Quirk, 2010). However, there is substantial heterogeneity in neuronal responses in these experiments, even within mPFC subregions (Baeg et al., 2001; Chang, Berke, & Maren, 2010; Fitzgerald, Giustino, Seemann, & Maren, 2015; Garcia et al., 1999; Giustino, Fitzgerald, & Maren, 2016; Peterson, 1986). Anxiety, as measured in elevated plus maze or open field testing or during restraint stress, also increases activation of PL neurons (Adhikari, Topiwala, & Gordon, 2010, 2011; Jackson & Moghaddam, 2006), and PL neurons encode the risk of punishment during a punished reward-seeking task (Park & Moghaddam, 2017).

Temporal dynamics of firing are important in aversive signaling. PL neurons fire at theta frequency during fear conditioning and anxiety (Adhikari et al., 2010, 2011; Dejean et al., 2016; Karalis et al., 2016), promoting the formation of task-relevant neuronal ensembles, and synchronizing activity with basolateral amygdala (BLA) and hippocampus (Adhikari et al., 2010; Dejean et al., 2016; Karalis et al., 2016; Padilla-Coreano et al., 2016). Synchronization is also associated with increased PL parvalbumin and somatostatin interneuron activity, which has been observed during fear conditioning, (Baeg et al., 2001; Courtin et al., 2014; Cummings & Clem, 2020). The interaction between PL and IL during fear conditioning and extinction is also important factor. PL and IL exhibit inhibitory interactions (Ji & Neugebauer, 2012; van Aerde, Heistek, & Mansvelder, 2008), though see (Marek et al., 2018). Some studies have shown that both PL and IL are activated during both fear conditioning and extinction, but the relative degrees of excitation and inhibition is important for determining the resulting emotional/behavioral response driven by mPFC outputs (Chang et al., 2010; Fitzgerald et al., 2015; Giustino et al., 2016).

Heterogeneity in PL and IL activity during fear conditioning and extinction may also result from the participation of these neurons in different afferent/efferent circuits. PL neurons projecting to BLA and periaqueductal gray (PAG) are activated during fear conditioning (Rozeske et al., 2018; Vander Weele et al., 2018). Connectivity between PL/IL and hippocampus and amygdala influences neuronal responses during anxiety and fear conditioning (Adhikari et al., 2010; Burgos-Robles et al., 2017; Dejean et al., 2016; Karalis et al., 2016; Klavir, Prigge, Sarel, Paz, & Yizhar, 2017; Padilla-Coreano et al., 2016). Neuromodulatory inputs from ventral tegmental area and locus coeruleus also influence neuronal responses and the behavioral output of mPFC during fear expression and/or extinction (Fitzgerald et al., 2015; Giustino et al., 2019; Vander Weele et al., 2018). These results indicate that continued analysis of circuit-level contributions may help resolve aspects of heterogeneous signaling observed related to aversive processing.

Neural activity associated with aversive processing may be particularly influenced by behavioral responses associated with the cues or outcomes. This has been shown during fear conditioning (Garcia et al., 1999; Halladay & Blair, 2015; Milad & Quirk, 2002), swim stress tests (Warden et al., 2012), and active avoidance (Diehl et al., 2018; Padilla-Coreano et al., 2019). Although most reports de-emphasize a purely motoric explanation of mPFC activity during fear conditioning, action may be a key factor that is integrated with emotional processing, memory consolidation, and recall, to produce the complex response properties seen at the single neuron level (Grunfeld & Likhtik, 2018). Given recent interest in characterizing active (e.g., avoidance) vs passive (e.g., freezing) responses to aversive stimuli (Fadok et al., 2017; Gruene, Flick, Stefano, Shea, & Shansky, 2015; LeDoux & Daw, 2018), understanding what role action plays in value-associated behaviors appears critical to our understanding of mPFC function.

4. Positive value: Reward and approach

The mPFC has also been well-characterized as a key brain region in signaling appetitive value and regulating appetitively-motivated behaviors (Hayes, Duncan, Xu, & Northoff, 2014). Appetitive signals in rodent mPFC have been described since at least the 1970s. Early reports demonstrated responses to delivered rewards (Ito & Olds, 1971) and cues conditioned to predict rewards (Olds, Disterhoft, Segal, Kornblith, & Hirsh, 1972; Pirch & Peterson, 1981). Interestingly, mPFC neurons responded to orally-consumed rewards such as food as well as to passively-received rewards such as brain stimulation. This suggests the possibility of positive value representation independent of its means of acquisition. Neurons recorded throughout the mPFC and ACC demonstrated selective responses to both intracranial stimulation and sucrose rewards, in some cases with the same neuron firing for both (Takenouchi et al., 1999). Along these lines, mPFC neurons, primarily those in PL, were active during outcome-alternating experiments where either food or water was presented after a delay (Miyazaki, Miyazaki, & Matsumoto, 2004). Approximately half of the neurons responded selectively to either food or water whereas the rest fired in anticipation of both. These results demonstrate the presence of both general positive valence signals and those encoding the identity of the rewarded outcome in mPFC neurons. Similar observations of reward- and reward-cue-related activity are found in both PL and IL subregions (Bouret & Sara, 2004; Le Merre et al., 2018; Otis et al., 2017; Valdes, Maldonado, Recabarren, Fuentes, & Torrealba, 2006). One possibility may be that value is represented in a graded fashion, with some neurons firing for more preferred rewards (e.g., sucrose) than others (e.g., water) (Petyko, Toth, Szabo, Galosi, & Lenard, 2009). Although variation in outcome magnitude, presumably correlating with value, has not been associated with mPFC firing

(Hong et al., 2019; Simon, Wood, & Moghaddam, 2015), neural correlates of value and individual preference have been observed under choice conditions (Sackett, Moschak, & Carelli, 2019). Comparably, mouse PL neurons recorded in a decision-making task signaled stimulus-driven value predictions, hypothesized to be compared with actual outcomes to promote adaptive behavior (Lak et al., 2020).

Studies of decision-making and spatial processing in the mPFC have reported high proportions of neurons responding during approach to or consumption of a food reward (Insel & Barnes, 2015; Lak et al., 2020; Pratt & Mizumori, 2001). However, multiple factors complicate interpretation of purely reward-related activity. One issue is the behavioral complexity associated with reward acquisition. During fear conditioning and other assays of aversive processing, negative outcomes are passively delivered, limiting explicit action demands (though see discussion of aversive outcome avoidance below). In contrast, rewards—particularly orally-ingested rewards—must be approached and consumed, raising the issue of whether neuronal activity changes represent value and/or action. This is more significant as behavioral complexity increases. Many studies demonstrating reward-related activity changes in mPFC do so during instrumental tasks where a lever-press or nosepoke delivers a food or liquid reward, which must then be acquired (e.g., Burgos-Robles, Bravo-Rivera, & Quirk, 2013; Homayoun & Moghaddam, 2006, 2009; Mulder, Nordquist, Orgut, & Pennartz, 2003; Peters, O'Donnell, & Carelli, 2005). Unsurprisingly, mPFC responses in these studies are complex, including those associated with predictive cues, instrumental responses, delay between response and outcome, reward approach, and reward consumption. Thus caution must be taken in interpreting neural signals related to appetitive value encoding as opposed to, e.g., behaviors associated with acquiring rewards.

As with aversive stimuli, there are differences in appetitive responses across PL and IL, although the exact nature of these differences has not been thoroughly characterized. Most studies investigating reward-related activity in mPFC subregions have focused on PL (or ACC), though reward-associated signals have been observed in IL (Burgos-Robles et al., 2013; Gentry & Roesch, 2018; Valdes et al., 2006). A few studies have compared PL and IL, reporting that PL responses are more associated with instrumental behaviors and IL responses are more related to reward anticipation/acquisition (Burgos-Robles et al., 2013; Takenouchi et al., 1999), although these differences may be more a matter of degree than category (Moorman & Aston-Jones, 2015). Response properties described across studies are heterogeneous. For example, PL neurons fire at the onset of reward-predicting actions such as lever presses (Peters et al., 2005), as well as during the time from action initiation to reward in a Go/NoGo task (Mulder et al., 2003). This diversity likely reflects a complex interaction of behavioral (task-dependence) and biological (specific region or neural circuit) variability.

Neuron phenotype also contributes to response heterogeneity. Most studies focus on characterizing pyramidal neuron activity or do not specify the neuron subtype recorded, but descriptions of interneuron activity have been reported. Some examples of interneuron responses include a relatively high proportion of sensory responses, reward approach and consumption, and reward/outcome evaluation (Insel & Barnes, 2015; Kvitsiani et al., 2013; Pinto & Dan, 2015). Importantly, the ability to target specific subtypes of interneurons (e.g., somatostatin vs parvalbumin) has revealed specific categories of response properties related to appetitive or aversive outcomes, described further below.

Neuronal connectivity is another parameter that plays a critical role in the response properties of mPFC neurons. As with neuronal responses to aversive outcomes, mPFC neurons projecting to different targets display different reward-related response properties. PL neurons projecting to NAc exhibited excitatory responses to a sucrose-predicting cue whereas PL projections to the paraventricular thalamus primarily responded with inhibition (Otis et al., 2017), revealing how commonly-observed diverse neuronal responses to the same cue or outcome are in part due signaling by separate populations defined by their anatomical projection target. These, and related results, e.g., (Ye et al., 2016), set the stage for future work that may explain functional heterogeneity seen in mPFC neuronal dynamics.

5. Drugs of abuse

mPFC responses during drug seeking are also diverse (Moorman, James, McGlinchey, & Aston-Jones, 2015). Early studies of cocaine and heroin self-administration characterized anticipatory responses, typically following a predictive cue or leading to the lever press, as well as post-drug delivery responses (Chang, Janak, & Woodward, 1998, 2000; Chang, Sawyer, Paris, Kirillov, & Woodward, 1997; Chang, Zhang, Janak, & Woodward, 1997; Rebec & Sun, 2005; Sun & Rebec, 2006). Activity in NAc-projecting IL neurons during cocaine seeking appeared to be inversely related to motivation for cocaine (Cameron, Murugan, Choi, Engel, & Witten, 2019), in line, to some degree, with the role of IL in facilitating extinction in fear conditioning and drug-seeking studies (Muller Ewald & LaLumiere, 2017; Peters, Kalivas, & Quirk, 2009). This suppressed activity lessened after an incubation period, arguing that one driver of increased motivation for cocaine is decreased inhibitory control by IL. A direct comparison of PL and IL neuronal responses to cocaine self-administration associated cues found responses in both PL and IL, but increased PL activation after a 30-day abstinence period, which produced increased motivation for cocaine (West, Saddoris, Kerfoot, & Carelli, 2014). These results indicate that PL and IL are both activated by cues predicting and behaviors directed toward drugs of abuse, but that the relative contributions of neurons in subregions or networks may shift over the course of abstinence/withdrawal.

mPFC activity has also been described in studies of alcohol use. The activity of dorsal PAG-projecting mPFC neurons recorded during alcohol consumption predicted future proclivity to compulsively consume alcohol under threat of punishment (Siciliano et al., 2019). Other studies have shown elevated overall mPFC neuronal activity, but blunted evoked responses, in alcohol-preferring "P" rats during cued alcohol drinking (Linsenbardt & Lapish, 2015; Linsenbardt, Timme, & Lapish, 2019; McCane et al., 2018), suggesting differential mPFC neuronal signaling based on alcohol preference. Subregion differences have also been observed in alcohol responses—although dorsal and ventral mPFC neurons were both activated during alcohol seeking, ventral, but not dorsal, neurons fired more during avoidance of alcohol-paired punishment (Halladay et al., 2020). The consistent finding of mPFC activation during drug and alcohol use indicates that a better understanding of the neural circuitry and dynamics of this system may improve our understanding and potential treatments of motivation-associated diseases such as drug and alcohol dependence, in addition to providing an additional perspective on value encoding in mPFC circuits.

6. Comparisons of positive and negative value

Most studies characterize either appetitive or aversive signaling by mPFC neurons in isolation, raising the question of whether mPFC neurons exhibit value selectivity when these outcomes are compared. In a small number of experiments, the same mPFC neurons have been recorded during presentation of both positive and negative cues and/or outcomes. During presentation of sucrose- or shock-predicting cues, rat PL neurons exhibited diverse response profiles, encoding most combinations of excitation and inhibition in response to both/either cues (Burgos-Robles et al., 2017). However, the predominant response was excitation to shock-predicting cues, and activity in this population of neurons was correlated with that in BLA neurons, suggesting a valence-selective population defined by its connectivity. Similar diverse responses in PL neurons were observed in response to unpredictable deliveries of either sucrose or tailpinch (Del Arco, Park, & Moghaddam, 2020). An approximately equal number of mPFC neurons responded to both sucrose and pinch, exhibiting both excitation and inhibition, and approximately 30% responded to both outcomes. Intraoral delivery of appetitive (sucrose or sodium chloride) or aversive (quinine or citric acid) solutions revealed a role for mPFC (broadly-defined) in encoding the intersection of palatability and tastant identity, with a bias in neural responses toward aversive tastants (Jezzini et al., 2013). Recordings from ACC neurons showed strong neuronal responses to food and shock, with some neurons firing under both conditions, hypothesized to reflect salience or attention signals (Schneider, Sciarillo, Nudelman, Cheer, & Roesch, 2020). In a separate study, a higher proportion of ACC neurons exhibited responses to shock vs reward, as well as to a neutral cue predicting no outcome (Caracheo, Grewal, & Seamans, 2018). Neurons also responded throughout blocks of trials, potentially revealing the use of valence to support representation of context (Hyman, Ma, Balaguer-Ballester, Durstewitz, & Seamans, 2012; Moorman & Aston-Jones, 2015). Emphasizing the role of network identity in response properties, PL neurons projecting to either NAc shell or dorsal PAG demonstrated differential signaling whereby most PAG-projecting neurons responded to shock and airpuff, and NAc-projecting neurons exhibited a mix of moderate responses to either shock or sucrose (Vander Weele et al., 2018). The lack of prominent PFC-NAc sucrose responding might be surprising given the results of (Otis et al., 2017), but may underscore the importance of context and behavioral components in shaping value-specific responses.

The cellular phenotype of mPFC neurons is also associated with response selectivity. In a reward/punishment go/no-go task, mouse PL neurons encoded multiple task parameters (Kamigaki & Dan, 2017; Pinto & Dan, 2015). Pyramidal neurons reflected diverse aspects of the task, with some response types differentially distributed across lamina, indicating an interaction with connectivity. Subtypes of GABAergic interneurons responded to different elements of the task (stimuli, outcomes, licking), indicating specific within-mPFC network correlates based on the intersection of cellular phenotype and extra-PFC connectivity. Differences across mPFC neuronal subtype were also observed in a reward foraging task, with somatostatin neurons encoding reward approach and parvalbumin neurons encoding disengagement (Kvitsiani et al., 2013). These data highlight the importance of cell-type identification to understand neural circuits associated with value encoding.

Other studies have compared mPFC activity during rewards and/or threats of punishments that can be avoided by withholding or performing an action. IL neurons exhibited a bias toward food-delivering, as opposed to shock-avoiding behaviors, even under extinction conditions, suggesting a privileged representation of positive reinforcement in IL (Gentry & Roesch, 2018). These data are aligned with previous work describing mPFC neuron activity during behaviors to acquire sucrose and ICSS, but not to avoid a shock (Takenouchi et al., 1999). Rostral PL neurons were inhibited during performance of platform avoidance of shock (Diehl et al., 2018), indicating that avoidance responses are regionally specific and may exhibit different dynamics than responses to inescapable shock-predicting stimuli. In a task where rats approached rewards or avoided/escaped from shock, PL neurons encoded complex combinations of stimulus identity, outcome valence, and behavioral response, in line with the concept of mPFC neurons exhibiting mixed selectivity (Fusi, Miller, & Rigotti, 2016; Rigotti et al., 2013), and in contrast with BLA neurons which showed stronger pure valence encoding (Kyriazi, Headley, & Pare, 2020). In a slightly different paradigm, in which rewarded outcome was associated with varying probabilities of shock, mPFC neurons were found to encode the risk of punishment though increases in baseline activity and decreases in action-associated responses and synchronous firing (Park & Moghaddam, 2017), demonstrating an intersection between valence and motivated action.

Together, these studies confirm that mPFC neurons respond to both positive and negative outcomes, even within the same task. Signals are heterogeneous and simultaneously encode value and action-associated parameters. Valence representation appears to be largely segregated, but occasionally overlaps at the level of the single neuron. Cellular identity and projection target may be key factors that identify which and how many variables are encoded. It will be of value in future studies to identify these correlates in tasks that can be directly compared, with matched actions and outcomes, in order to identify how combinations of factors are encoded at the level of neurons or populations (Fig. 1).

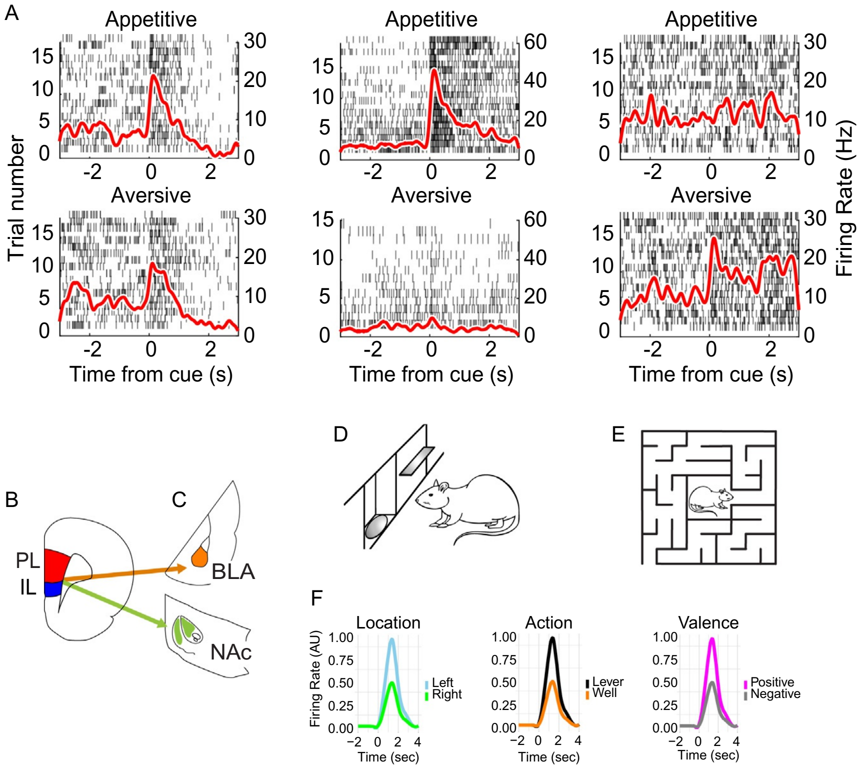

Fig. 1 What factors may explain apparent heterogeneity in mPFC neuron value signaling? (A) Three example mPFC neurons (from Kaminska and Moorman, in prep.) responsive to both appetitive and aversive outcome-predicting cues (left), only appetitive cues (middle), or only aversive cues (right). (B–F) Schematics of potential explanations for diversity in mPFC value encoding. (B) Subregion differences (e.g., different responses in PL vs IL neurons), (C) Differences in afferent projection target (e.g., different responses in neurons projecting to BLA vs NAc), (D) Differences in actions (e.g., neurons may respond to behaviors such as lever-press vs well-entry instead of or in addition to outcomes), (E) Potential cognitive factors (e.g., neurons may respond to variables associated with decision-making, learning, navigation, etc.), (F) Heterogeneous signaling (e.g., mixed selectivity) whereby individual neurons encode unique combinations of value, action, cognition, etc., at different strengths.

7. Integration of value and action

Not included above are numerous studies with goals beyond understanding direct relationships between mPFC neuronal activity and value. This includes studies such as those related to cognition, action control and social behavior. Reward or outcome related signals have been described in many of these studies, e.g., (Del Arco et al., 2017; Gruber et al., 2010), indicating that mPFC neurons encode some aspect of value, even when this is not the main focus of the experiment.

This highlights the point that signals related to multiple task parameters overlap during any behavioral test. Animal behavior is almost always motivated by potential rewards or punishments, producing a persistent motivational signal that may be hard to extract from neural signatures of cognition or behavior. Conversely, as demonstrated by many studies discussed above, it is challenging to extract pure value signals from mPFC neurons (Bissonette, Gentry, Padmala, Pessoa, & Roesch, 2014). Although mPFC neurons respond to positive or negative stimuli, it is challenging to identify value signals in the absence of any other factor driving activity. One major confounding factor is the behavior required to obtain or avoid an outcome. In some cases, what appear to be reward-related signals may actually be more closely associated to actions such as licking and consumption-related behavior, even when reward is not delivered (Amarante, Caetano, & Laubach, 2017; Horst & Laubach, 2013). These motor-related signals appear to be modulated by motivation levels (de Haan et al., 2018), suggesting that both value and action are represented in mPFC neuronal activity.

One framework for investigating the intersection of value and action is characterizing activity related to goal-directed vs habitual behaviors. Overtraining transitions animals from a goal-directed (outcome-devaluation sensitive) to habitual (devaluation insensitive) behavioral strategy. Over the course of overtraining, IL neurons gradually increased, and PL neurons decreased, activity (Smith & Graybiel, 2013). Using a lever-based operant task, changes in IL activity were also observed after extensive training on a random interval, habit-associated task (Barker, Glen, Linsenbardt, Lapish, & Chandler, 2017). The details of the neuronal responses varied between these studies (e.g., excitation vs inhibition, task epoch, etc.), but the results reflect differences in mPFC neuronal activity based on whether behaviors are goal-directed vs habitual.

The observation that mPFC neurons integrate action and outcome should not be surprising. Reward, fear, action, learning, attention, and other aspects of cognition and behavior are interlinked. Adaptive behavior, broadly construed, is a result of the seamless integration of these variables to allow responses to exogenous and endogenous stimuli. From an evolutionary and ethological perspective this is intuitive. Rewards (food, mates, shelter) must be acquired and punishers (noxious stimuli, threats, dangerous environments) must be avoided. This is dependent on calculating outcome costs and values, orienting to goals, performing actions, and learning from results. Actions themselves are costly and performance of actions (at least when goal-directed) must be evaluated in the context of the value of an outcome. So value computations are inherently built into almost all actions.

8. Summary and conclusions: Value, actions, both, or neither?

As is clear from the extensive studies described above, neuronal activity in mPFC appears to be strongly influenced by both positive and negative value. These value representations include responses to outcomes (e.g., food rewards, shocks), cues that predict outcomes, actions associated with acquiring or avoiding outcomes, and combinations of all of these. Based on the frequency of their observations, it seems logical to conclude that value signals make up a predominant component of mPFC function. However, a number of caveats suggest caution in this interpretation (see Box 1). The vast

BOX 1 Information needed to help refine understanding of value coding in mPFC.

Experimental design

- ○ Account for behavioral variables (lever press vs freeze, etc.)
- ○ Account for cognitive variables (salience/attention, decisions, learning, etc.)
- ○ Precise measurement of behaviors to account for unanticipated behavioral correlates (video analysis, EMG, etc.)
- ○ Parameterize outcomes (sucrose concentration, shock vs airpuff, etc.)
- ○ Compare behaviors across studies

Biological sources of functional heterogeneity of value responsive neurons

- ○ Anatomical location (PFC subregions)
- ○ Connectivity (afferent & efferent)
- ○ Cellular differences (pyramidal vs interneuron subtypes)
- ○ Molecular and genetic differences (receptors and other signaling proteins, transcription factors and other genetic regulators)

Mechanisms of encoding

- ○ Ensemble vs single-neuron selectivity
- ○ Mixed selectivity (how heterogeneous? what are the parameter axes?)
- ○ Integration of response properties with biological factors
- ○ Contributions of dynamics (epochs of excitation or inhibition, temporally patterned activity, coherence with LFP)
- ○ Encoding plasticity—do mPFC neurons always respond to valued outcomes the same way?

majority of the studies described above measured neural responses to one type of outcome in isolation. Most studies characterizing mPFC responses to footshocks do not also probe responses to sucrose, and vice versa. In the absence of parametric manipulation of value, it is challenging to conclude that a response associated with a particularly-valued outcome is in fact a value representation as opposed to, for example, a salience representation or the representation of an action associated with the outcome such as an approach or avoidance. The few studies directly comparing positive and negative outcomes clearly demonstrate neuronal responses to both with different biases (more positive or more negative) depending on the study. Although these studies advance our understanding of value representation by contrasting positive and negative outcomes they, too, are challenged by differential levels of salience and different actions, both of which may be main drivers of mPFC function. So, for example, delivery of a shock may be more salient or intensely negative than delivery of sucrose is positive. As such, differential representations within or across neurons may have alternate foundations than positive or negative value per se. Similarly, the actions associated with each outcome differ, as noted above. In order to make a clear association between mPFC neuronal activity, future studies need to incorporate parametric manipulations of outcomes and control for, or closely monitor, behaviors associated with different outcomes (Box 1). Forming conclusions based on these manipulations may even prove challenging, as there is a close relationship between outcome value, such as high vs low sucrose concentration, and value-associated actions, such as intensity of consumption (Amarante et al., 2017). For now, we are left with the overarching observation that mPFC neurons respond when outcomes of a particular valence (or predictors of such outcomes) are presented. But it is difficult, if not impossible, to say with confidence that such responses are specifically reflecting value as opposed to multiple other potential associated factors.

So should we consider an alternate interpretation—for example, that mPFC signals are best explained by actions associated with outcomes but not values? It is equally challenging to confidently make this conclusion, or related conclusions such as value representations being best described by the salience of cues or outcomes. In most of the studies described above, actions are motivated—freezing occurs in response to a shock-predicting cue, and approach or consumption is driven by an appetitive outcome. Thus, the value of an expected outcome is a frequent driver of action, even when the goal of a study is to characterize action-associated mPFC activity. In the same way that it is hard to isolate value in the absence of other factors, it is challenging to identify neural correlates of action in the absence of parameters driving such actions. In some sense, studies of goal-directed vs habitual behavior may permit some insight into this, under the assumption that habitual behaviors are actions in the absence of any expected outcome, though it is notable that mPFC neuronal activity is different under goal-directed vs habitual conditions, as described above. This indicates that actions, independent of their goals or the context surrounding them, are not the exclusive focus of mPFC activity and that some aspect of expected outcomes, or the absence of such expectations, influence mPFC neuronal activity.

The sections above describe a large number of studies in which neurons respond during situations in which outcomes have a valence. Few, if any, conclusively identify a "pure" value signal or, conversely, a "pure" signal related to action, salience, or other parameter that reliably explains variations in mPFC neuronal activity across studies. In some sense this is disappointing—it would be quite satisfying to align the research to date and conclude that the results together indicate a specific role for mPFC circuits in any one of these aspects of behavior. And yet we probably shouldn't be surprised that there is no single encoded variable in mPFC neuronal activity. Further, we should be encouraged that there are clear paths forward to refine our understanding of the presence or absence of value encoding in mPFC. For example, controlling for behavior across outcomes, varying salience within and across outcomes of different valence, and more (see Box 1). It would be disheartening to think that we have exhausted our potential manipulations and are still left with inconclusive results. Instead, there are obvious experiments, either underway or waiting to be done, that will answer some of these questions for us. When these behavioral controls are applied to studies incorporating biological heterogeneity across mPFC neurons (e.g., responses of NAc-projecting vs BLA-projecting neurons) we will have the opportunity to identify the extent of behavioral encoding with greater precision has been previously possible.

The intersection of value with so many other aspects of behavior raises an alternate perspective in which value is not directly encoded by individual neurons but is an emergent property of network activation. Neural responses related to value are distributed throughout the brain (Hunt & Hayden, 2017; Vickery, Chun, & Lee, 2011). mPFC may be a node within a larger value calculation network, and individual neurons may participate in the representation of value without being specifically dedicated to value encoding. Similarly, mPFC neurons may simultaneously encode other functions as well, as demonstrated by the large numbers of behavioral and cognitive factors that are associated with mPFC neuronal activity (Cassaday et al., 2014; Euston et al., 2012). This framework dovetails with the conceptualization of mPFC neurons exhibiting mixed selectivity, responding in a nonlinear fashion to multiple sensory, behavioral, or cognitive parameters (Fusi et al., 2016; Grunfeld & Likhtik, 2018; Rigotti et al., 2013). Although responses to value may be detected in a study in which it is probed (e.g., neural responses to sucrose presentation), a full characterization of the representational suite of each neuron may depend on multiple tests to identify the extent of response selectivity. An additional important future direction for understanding how mPFC neurons encode value with respect to other variables is to integrate functional, anatomical, and molecular properties of mPFC neurons (Ye et al., 2016), as subpopulations of neurons may exhibit more restricted selectivity. Some studies have characterized limits of mixed selectivity using model-free clustering and network identification of neuron subpopulations (Hirokawa, Vaughan, Masset, Ott, & Kepecs, 2019), suggesting that functional categories of prefrontal neurons may exist once properly classified.

Perhaps a more extreme conceptualization is that the representation of value is epiphenomenal at the level of the single neuron or even neuronal ensembles. This perspective is rooted in questions of whether the psychological concepts that we experience and test experimentally are actually represented at the level of neurons or neural networks (Buzsaki, 2020; Churchland, 1981; Hunt & Hayden, 2017). In some sense, this aligns with reframing value through the lens of a classical characterization of value inferred through action—reinforcers produce approach, and punishers produce avoidance. Positive value, for example, might simply be a term used to describe a stimulus that produces approach more strongly than another. By this logic, neural representation of value-associated stimuli (reward- or punishment-predicting cues in the lab) might be general association signals that could be equally applied to non-valued outcomes that produce similar behaviors, draw attention, or produce outcome-related learning.

Ultimately, animals are able to make preference-based decisions, presumably through assigning value to objects and action outcomes, and to execute and adjust their behaviors based on these decisions and outcomes. In the brain there must be some type of computation that permits these associations to be made (Vlaev, Chater, Stewart, & Brown, 2011). Given the studies described above, and despite the caveats above, neurons in the mPFC likely participate in this process. Instead of exclusively processing value information, mPFC neurons may encode value when it is critical to drive behavior, consistent with the region's role in decision-making and flexible (i.e., cost/benefit-driven) behaviors. mPFC may also use value to generate a representation of context (Hyman et al., 2012; Moorman & Aston-Jones, 2015), or to support learning and memory recall (Euston et al., 2012). One possible conclusion permitting a function for explicit value representations is that value signals may be present in a subset of mPFC neurons (defined, perhaps, by shared anatomical or other cellular features), in the service of complex representations at the ensemble level so that the maximum amount of world information can be used to guide behavior. Despite impressive studies revealing the presence of value-related signals in mPFC, exactly how mPFC neurons, within specific subregions and circuits, integrate this information is still unclear. The widespread, and growing, interest in mPFC coding befits its role as a highly connected structure where neurons exhibit complex response properties in the service of complex flexible value-motivated behavior. When this interest is paired with experiments designed to optimally extract value (or action, or other) signals, there is a significant chance of identifying the presence or absence of pure value signals and, in doing so, reveal core neuronal principles underlying behavioral control.

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