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Prefrontal Dopamine in Associative Learning and Memory

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Abstract

Learning to associate specific objects or actions with rewards and remembering the associations are everyday tasks crucial for our flexible adaptation to the environment. These higher-order cognitive processes depend on the prefrontal cortex (PFC) and frontostriatal circuits that connect areas in the frontal lobe with the striatum in the basal ganglia. Both structures are densely innervated by dopamine (DA) afferents that originate in the midbrain. Although the activity of DA neurons is thought to be important for learning, the exact role of DA transmission in frontostriatal circuits during learning-related tasks is still unresolved. Moreover, the neural substrates of this modulation are poorly understood. Here, we review our recent work in monkeys utilizing local pharmacology of DA agents in the PFC to investigate the cellular mechanisms of DA modulation of associative learning and memory. We show that blocking both D1 and D2 receptors in the lateral PFC impairs learning of new stimulus-response associations and cognitive flexibility, but not the memory of highly familiar associations. In addition, D2 receptors may also contribute to motivation. The learning deficits correlated with reductions of neural information about the associations in PFC neurons, alterations in global excitability and spike synchronization, and exaggerated alpha and beta neural oscillations. Our findings provide new insights into how DA transmission modulate associative learning and memory processes in frontostriatal systems.

Keywords

prefrontal cortex; dopamine receptors; learning and memory; neural oscillations; macaque monkey

Introduction

Learning to identify and remember rewarding and aversive stimuli in our environment is key to our advanced cognitive abilities and to our survival. Associative learning and memory processes are not only crucial for a simple classification of food as appetitive or unpleasant but also to know what outcomes will follow our actions. This type of goal-directed

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associative learning and memory depend heavily on the prefrontal cortex (PFC) and interactions between the PFC and other subcortical structures such as the striatum (Miller and Cohen, 2001; Fuster, 2001; Graybiel, 2008). Neurophysiological studies show changes in PFC neural activity during learning and memory tasks (Asaad et al., 1998; Histed et al., 2009; Pasupathy and Miller, 2005; Benchenane et al., 2010; Antzoulatos and Miller, 2011, 2014; Puig and Miller, 2012, 2014), and damage to the PFC elicits profound learning, memory, and other cognitive deficits (Godefroy, 2003; Robbins, 2007; Kehagia et al., 2010). Furthermore, learning and memory impairments are found in psychiatric and neurological disorders associated with abnormalities in PFC transmission such as schizophrenia (Park and Holzman, 1992; Elvevåq and Goldberg, 2000).

The PFC is innervated by dopamine (DA) axons originating in the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) (Fallon, 1988; Goldman-Rakic et al., 1992; Williams and Goldman-Rakic, 1998; Levitt et al., 1984; Lewis, 1992; Björklund and Dunnett, 2007; Yetnikoff et al., 2014), that modify PFC function via the D1 and D2 families of receptors (D1R and D2R, respectively) (Seamans and Yang, 2004). Selective DA depletion in the PFC of macaque monkeys produces deficits in executive function (Brozoski et al., 1979). In fact, disruption of PFC DA transmission is suspected to underlie a number of psychiatric conditions including schizophrenia, depression, and attention deficit hyperactivity disorder (Grace, 1991; Robbins, 2000a, 2000b; Arnsten et al., 2009, 2010; Winterer and Weinberger, 2004).

Studies conducted in non-human primates have revealed that DA neurons carry out computations that support associative learning and memory. More specifically, they compute reward prediction errors that allow them to keep track of stimuli associated with rewards. However, the functional connection between PFC DA and learning is not straightforward considering that the PFC is an associational area that integrates information from numerous cortical and subcortical structures and receives axons from other neuromodulatory cores such as the serotonergic and noradrenergic systems (Clarke et al., 2004; Ramos and Arnsten, 2007; Celada et al., 2013; Robbins and Arnsten, 2009; Puig and Gulledge, 2011). Therefore, the exact role of PFC DA signals during associative learning and memory awaits full elucidation.

Over the last fifteen years or so, sophisticated electrophysiological techniques have been developed to allow the simultaneous recording of neural activity from multiple sites in awake behaving animals. These techniques, in combination with computational approaches, have advanced our understanding of the neural substrates of complex cognitive tasks such as learning and memory. This includes the decoding of the spiking pattern of single neurons as well as the interaction of networks of neurons reflected as neural oscillations or 'brain waves'. Here, we review our recent work in monkeys on the neural substrates of learning and memory in frontostriatal systems, and the important role of DA transmission in its modulation.

The Dopaminergic System in Frontostriatal circuits

Anatomy of the Dopaminergic System in Prefrontal Microcircuits

In primates, the PFC receives inputs from DA axons originating in the VTA and the SNc that form two bands innervating superficial (II-III) and deep (IV-V) cortical layers (Goldman-Rakic et al., 1992; Williams and Goldman-Rakic, 1998; Levitt et al., 1984). The dopaminergic innervation of the PFC is very delicate and not dense, especially when compared to striatum or motor cortex. DA modifies PFC function via D1-like receptors (D1R and D5R subtypes) and D2-like receptors (D2R, D3R, and D4R subtypes). Both families are G-protein-coupled receptors that exert slow changes of activity in the cell and act as functional neuromodulators. D1R show low affinity for DA, whereas D2R show high affinity (Seamans and Yang, 2004). PFC neurons express the D1R and D4R DA receptor subtypes, whereas D2R, D3R, and D5R are present but to a much lesser extent, especially D3R (Lidow et al., 1991; de Almeida et al., 2008; Seamans and Yang, 2004). D1R and D4R mRNAs have a widespread distribution in several cortical layers, whilst D2R and D5R mRNAs are preferentially confined to layer V (de Almeida et al., 2008). All receptors have been found in pyramidal neurons and inhibitory interneurons of the PFC (Santana et al., 2009; Mrzljak et al., 1996; Glausier et al., 2009; Bordelon-Glausier et al., 2008; Muly et al., 1998; De Almeida and Mengod, 2010; De Almeida et al., 2008; Le Moine and Gaspar, 1998).

In mice, separate populations of layer V pyramidal neurons of the medial PFC with unique morphological and physiological properties preferentially express only D1R or D2R (Gee et al., 2012; Seong and Carter, 2012). Interestingly, the D2R-expressing layer V pyramidal neurons project largely to the thalamus (Gee et al., 2012), suggesting a specific contribution of PFC D2R to frontostriatal circuits. We note that the mouse medial PFC is not entirely homologous with the monkey lateral PFC, indeed some of the layer V neurons in mice appear to combine properties of layer V and layer III neurons in primate. Nevertheless, this anatomical distribution of D1R and D2R in layer V of the mouse medial PFC bears some resemblance to the direct and indirect pathways in the basal ganglia, where medium spiny neurons in the striatum selectively express D1R or D2R, respectively, with unique roles in associative learning (see below; Albin et al., 1989; Alexander and Crutcher, 1990; Smith et al., 1998; Gerfen and Surmeier, 2011). However, the involvement of discrete D1R- or D2R-expressing PFC networks in learning and memory has yet to be reported.

The Dopaminergic System in the Basal Ganglia and their Involvement in Associative Learning

A review of associative learning would be remiss without some discussion of the role of the basal ganglia (BG). Because there have been several excellent reviews on the BG over the last few years (e.g., Calabresi et al., 2014; Gerfen and Surmeier, 2011; Lerner and Kreitzer, 2011; Seger, 2013), we will herein only present a brief overview. The BG are an evolutionarily conserved set of subcortical nuclei, which play a well-established role in motor control. Even though they do not initiate motor movements, they exert a powerful regulation of when and what motor movements will be executed. Hence, their function has been most concisely described as action selection. The action selected by the BG can be

shaped over repeated trials by reward, which makes them prominent contributors to procedural and habit learning (Knowlton et al., 1996; Packard and Knowlton, 2002).

The functional organization of the BG seems to follow two different but not mutually exclusive principles: That of the two opposing pathways and that of the multiple parallel loops (see below). The most influential model of the BG organization involves two, largely opposing pathways: the direct and the indirect (Albin et al., 1989; Alexander and Crutcher, 1990). Both of these pathways originate in the striatum (the input structure of BG), which comprises of the caudate nucleus (CN), the putamen, and the ventral striatum (nucleus accumbens). The principal striatal neurons, the medium spiny neurons, receive strong dopaminergic inputs from SNc and VTA, and excitatory input from widespread areas of the cerebral cortex, as well as the thalamus and other subcortical sources. The same neurons also constitute the main projection neurons from the striatum, sending their inhibitory, GABAergic projections exclusively to targets within the BG, namely the globus pallidus and the SN. The medium spiny neurons that belong in the direct pathway express predominantly the D1R (Gerfen and Surmeier, 2011), and project their inhibitory output directly to the globus pallidus pars internus (GPi) and the SNr (DeLong, 1990). Because GPi and SNr tonically inhibit their thalamic, midbrain and brainstem targets, activation of the direct pathway leads to release of the BG targets from inhibition. In contrast, the medium spiny neurons that belong in the indirect pathway express predominantly the D2R, and project their inhibitory output to the globus pallidus pars externus (GPe). This leads to disinhibition of the subthalamic nucleus (the primary GPe target and source of excitatory inputs to GPi and SNr), and consequent enhancement of the GPi- and SNr-mediated inhibition of the BG targets: the opposite, that is, effect to activation of the direct pathway. A third pathway (the hyperdirect pathway) is not covered here because it partly overlaps with the indirect and has the same functional endpoint (Mink and Thach, 1993): enhanced inhibition of the BG targets. Their distinct anatomical connectivity and dopaminergic input bestows the direct and indirect pathways with unique roles in associative learning. Rodent studies of slice neurophysiology have indicated that coincident activation of the glutamatergic receptors of corticostriatal synapses with activation of the D1R by dopamine can lead to long-term potentiation (LTP) of the active corticostriatal synapses, thus reinforcing the specific cortical input to these striatal neurons (Shen et al., 2008). In the presence of adenosine or acetylcholine however, instead of dopamine, activation of these corticostriatal synapses can lead to their long-term depression (LTD; Lerner and Kreitzer, 2011), which can serve as punishment of the action these inputs promoted. In contrast, coincident activation of the glutamatergic and the D2R receptors can lead to LTD of the active corticostriatal synapses, thus suppressing the particular cortical inputs to the indirect-pathway striatal neurons (Shen et al., 2008). In turn, activation of the NMDA receptors in the presence of adenosine instead of dopamine, can lead to LTP of these synapses. The picture that emerges from the two-opposing pathway organization of the BG, is, therefore, that, across multiple repetitions of trial-and-error learning, the corticostriatal signals that are consistently paired with reward will become more potent in commanding the direct pathway (thus releasing the appropriate response to the stimulus), and less potent in engaging the indirect pathway (and in interfering with the appropriate response to the stimulus). The reverse will be true if these inputs are not paired with reward. Consistent with this model, a recent study in mice

demonstrated that selective (optogenetic) activation of D1R-expressing neurons in the striatum induces persistent reinforcement, whereas selective activation of D2R-expressing neurons induces transient punishment (Kravitz et al., 2012).

The second organizational principle of BG is that of the parallel, segregated loops (Alexander and Crutcher, 1990; Graybiel, 2008). It has long been known that the information that enters the BG, and is processed by them, does not spread homogeneously across the entire BG through lateral connections. Rather, it propagates vertically: Starting with the striatum and going through the entire BG, each BG nucleus has functionally distinct regions, which communicate with the corresponding regions of the upstream and downstream BG nuclei. Because the output signals from the BG tend to reach the same brain regions from which the BG inputs originated, these pathways have been conceptualized as parallel, segregated loops. The anatomical distinction among them is most easily seen in the striatum: The CN, along with the anterior putamen, primarily process executive signals originating from the prefrontal and posterior parietal cortices, and belong in the executive (also called associative) loop. The posterior putamen primarily processes signals coming from the primary motor and premotor cortices, and belongs in the motor (or sensorimotor) loop. Finally, the ventral striatum receives signals originating from limbic brain areas, such as the amygdala, hippocampus, orbitofrontal and medial prefrontal cortices, and belongs in the limbic (or motivational) loop (Graybiel, 2008). The exact extent to which these parallel loops interact with each other inside the BG is not fully understood, but there is evidence that under certain conditions, there may be a transition of the behavioral control from the executive to the sensorimotor loop (Ashby et al., 2010). In rodents, selective lesions of the sensorimotor striatum switches control of a learned behavior from habitual to goal-oriented mode, which is considered to be under control of the executive loop (Yin et al., 2004). In monkeys, learning new motor sequences engages more neurons in the executive than the sensorimotor striatum, whereas the reverse is true for performance of overlearned sequences (Miyachi et al., 2002). In humans, the early vs. late stages of procedural learning selectively activate the executive vs. sensorimotor striatum, respectively (Lehericy et al., 2005). It seems, therefore, that the early stages of reward-driven associative learning rely on information processing in the executive loop, while automatic performance of well-learned associations relies on the sensorimotor loop. Further below, we review a series of studies we conducted to advance our understanding of the different roles that PFC and CN (the key components of the executive loop) may play in associative learning. Next, we examine the contribution of the limbic loop.

The goal-directed selection of an action rests not only on the association of stimuli with responses (which, as mentioned, seems to be the domain of the executive and sensorimotor loops), but also on the evaluation of the response outcome. The latter seems to be contributed by the limbic loop, a key component of which (outside the BG and PFC) is the amygdala. Even though the amygdala has been traditionally associated with fear learning, previous studies have indicated that it also processes the positive value of stimuli, i.e., reward (Baxter and Murray, 2002). The basolateral amygdala (BLA), in particular, form strong reciprocal connections with the medial and orbital PFC both directly and indirectly, through the mediodorsal thalamic nucleus (which communicates with the PFC; Price et al., 1996). A series of studies in humans, monkeys, and rodents have indicated that the network

between medial PFC, orbital PFC, and BLA is critical for the evaluation of the stimulus that would follow a chosen action (Baxter and Murray, 2002; Griffiths et al., 2014). Activation of human BLA neurons in response to food items scales with their monetary value (Jenison et al., 2011). In both humans and animals, lesions of the BLA, the associated PFC regions, or their connecting pathways, diminish the ability to adapt choices to the dynamic value of action outcomes (Balleine et al., 2003; Camille et al., 2011; Zeeb and Winstanley, 2013). It is hypothesized, therefore, that the BLA-PFC network computes the value of an action's predicted outcome, and feeds it to the BG through the ventral striatum, which can then weigh in, through the aforementioned direct and indirect pathways, at the selection from the alternative actions.

Interactions between the Basal Ganglia and the Prefrontal Cortex during Associative Learning

As mentioned above, the learning of new associations involves the executive loop, which primarily includes the PFC and CN. In order to dissect their distinct contributions to associative learning, our lab recorded from these two areas during stimulus-response (SR) learning. In a study that examined the learning of SR reversals (Pasupathy and Miller, 2005) it was seen that the CN reverses the associations (i.e., the CN neural signals better predict the correct response to each stimulus after reversal) early on, before PFC does. Over several trials of the reversed associations, the PFC signals also start predicting the correct motor response to the stimulus, at levels comparable to the CN signals. This result is consistent with the previously hypothesized hierarchy between PFC and striatum for associative learning: The strong and topographically organized reward-predicting dopaminergic signals in striatum support relatively rapid representation of SR associations, whereas long-term plasticity in PFC requires more extensive training which leads PFC to integrate more experiences before updating its representations (Houk and Wise, 1995). In a subsequent experiment (Antzoulatos and Miller, 2011, 2014), we tested the same PFC-CN module in reward-driven category learning. The animal was first trained to associate individual stimuli (i.e., category exemplars) with one of two alternative saccades, and as these associations were being learned, the number of stimuli associated with each response was progressively increased. Because all stimuli mapping to the same response were exemplars of the same perceptual category, after sufficient exposure to these stimuli, the animal could extract the essence of the two categories and accurately predict which response to a completely novel stimulus would lead to reward. The results of that study suggested that not all associative learning progresses faster in BG than in PFC. Although the CN did display the predicted superiority over PFC during the learning of individual associations, there was a reversal of the roles during the exposure to multiple stimuli and the learning of the categories: only PFC signals used the category membership of a novel stimulus to predict the appropriate response, while CN signals encoded the imminent response only shortly before it was executed. These results suggest a potential dissociation between the PFC and BG in reward-driven associative learning: when the associations can only be gradually learned, through many repetitions of the same experience, the BG are better equipped to acquire the representation of the association, which can then support the associative learning in the PFC. When, however, new associations can be generalized from past knowledge without much practice, PFC is better equipped than BG to integrate the new with the old learning.

Neural substrates of Associative Learning and Memory: Dopamine Neurons

Extensive research undergone in the last couple of decades has revealed that the spiking patterns of DA neurons may play critical roles in the neural mechanisms underlying reward-based learning (Schultz, 1998, 2007, 2013). Most DA neurons show phasic activations (bursts of action potentials) that evoke transient high amplitude DA release (Floresco et al., 2003; Grace, 1991; Grace and Bunney, 1984a; Grace et al., 2007; Goto et al., 2007) following unpredicted rewards coding a quantitative 'prediction error' signal, namely the difference between received and predicted reward value. A reward that is better than predicted elicits an activation (positive prediction error response), a fully predicted reward draws no response, and a reward that is worse than predicted induces a depression of activity (negative error response) (Schultz, 1998, 2007, 2013). This type of DA neurons encode motivational value, they are excited by rewarding events and inhibited by aversive events (Bromberg-Martin et al., 2010; Matsumoto and Hikosaka, 2009). With learning, these phasic DA responses transfer from primary rewards to reward-predicting sensory cues (Schultz et al., 1993), likely broadcasting a 'teaching signal' to their target brain areas. These neurons support brain systems for seeking goals, evaluating outcomes, and value learning, such as the dorsal striatum, the nucleus accumbens, and the orbitofrontal cortex. In fact, the nucleus accumbens shows especially high levels of reward-predicting neural activity (Cheer et al., 2007; Owesson-White et al., 2009) and rapid DA release consistent with this reward predicting signals of DA neurons during associative learning (Day et al., 2007; Phillips et al., 2003). Moreover, motivational-value coding DA neurons could provide an ideal instructive signal for striatal circuitry involved in value learning, such as learning stimulus-response habits (Bromberg-Martin et al., 2010). In addition, a second type of DA neurons encode motivational salience, they are excited by both rewarding and aversive events and have weaker responses to motivationally neutral events, providing appropriate instructive signals to detect, predict, and respond to situations of high importance (Bromberg-Martin et al., 2010; Matsumoto and Hikosaka, 2009). These neurons support brain systems for orienting of attention, cognitive processing, and general motivational drive, such as the dorsolateral PFC and the dorsal striatum. Consistently with this hypothesis, studies conducted in the lateral PFC of monkeys have shown both increases of DA release in response to a punishment of water when monkeys were expecting juice (Kodama et al., 2014) and subpopulations of neurons that are excited by both rewarding and aversive visual cues whose activity correlates with better performance in a working memory task (Kobayashi et al., 2006). In addition to their value- and salience-coding activity, both types of DA neurons also transmit an alerting signal, triggered by unexpected or novel sensory cues of high potential importance. Together, a cooperation between the information about the value of reward-predicting stimuli (appetitive vs. aversive), its salience, and alerting signals may allow the use of specific neural signals to selectively reinforce or avoid behaviors.

DA neurons also exhibit tonic firing driven by pacemaker-like membrane currents (Grace and Bunney, 1984a; Grace and Bunney, 1984b; Grace, 1991; Goto et al., 2007). Aversive stimuli and the omission of expected rewards induce transient suppression of tonic spiking in DA neurons (Ungless et al., 2004; Tobler et al., 2003), implicating this spiking pattern in

learning as well. Recent work has shown that DA release in the striatum increases gradually (ramps up) as rats expect distant rewards, perhaps providing motivational drive (Howe et al., 2013) or encoding uncertainty (Fiorillo et al., 2003). Yet again, these types of signals have not been investigated in PFC.

An emerging idea is that the heterogeneity in DA neurons' activity patterns is related to their involvement in distinct anatomical circuits. Although DA neurons in the VTA and SNc show some similarities in encoding reward and aversion (Ilango et al., 2014), they receive anatomical inputs from distinct brain regions (Watabe-Uchida et al., 2012). In particular, DA neurons' contribution to reward or aversion seems to depend on whether they are activated from the laterodorsal tegmentum or the lateral habenula, respectively (Lammel et al. 2012), or whether they are located in the dorsal or ventral aspects of the VTA or SNc (Brischoux et al., 2009; Matsumoto and Hikosaka, 2009; see for review Bromberg-Martin et al., 2010). These studies reveal the complexity of DA neurons' computations and anatomy, and future work will be necessary to fully comprehend the nature of their involvement in learning and memory.

Neural substrates of Associative Learning and Memory: Prefrontal Neurons and Networks

Prefrontal Dopamine in Associative Learning and Memory

As described earlier, the PFC and striatum are involved in reward-based associative learning (Puig and Miller, 2012, 2014; Antzoulatos and Miller, 2011; Histed et al., 2009; Pasupathy and Miller, 2005; Asaad et al., 1998; Graybiel, 2005; Costa, 2011). In order to study the neural substrates of this circuit during learning, we trained monkeys to learn by trial and error associations between visual cues and saccades to specific targets. With learning, as the monkeys were increasingly able to predict which saccade would yield a reward, many prefrontal and striatal neurons increased spiking during the cue presentation and/or the memory delay that predicted their preferred saccade or decreased their activity for the non-preferred saccade (Figure 1 and Pasupathy and Miller, 2005). Importantly, these learning-related changes in spiking activity occurred at different rates in PFC and striatum. They initiated in striatum, where changes were rapid compared with a slower trend observed in the PFC (Pasupathy and Miller, 2005; Antzoulatos and Miller, 2011). This supports the view that during trial-and-error learning the BG initially identifies rewarded associations and instructs the PFC to trigger slower learning mechanisms of more abstract rules that drive behavioral performance (Pasupathy and Miller, 2005).

As mentioned above, it is likely that the DA released into the lateral PFC by salience-encoding DA neurons likely plays a role in associative learning. Along these lines, we have recently shown that D1R and D2R in the lateral PFC contribute to associative learning but not memory of familiar associations (Puig and Miller, 2012, 2014). Macaque monkeys performed an oculomotor learning and memory task similar to the task used by Pasupathy and Miller (2005). They learned new and remembered highly familiar associations between visual cues and saccades to a right or left target (Figure 2A, B). For each recording session, monkeys learned associations between two initially novels cues and saccades to the left or

right and also performed well-practiced associations with two familiar cues. We tested the effects of local injections of DA antagonists as well as saline controls.

Local injections of small amounts of a D1R or a D2R antagonist (SCH23390 and eticlopride, respectively) into the lateral PFC impaired learning and cognitive flexibility. Monkeys needed more trials to learn the associations (learning curves and learning rates were reduced) and more often repeated the same error on successive trials (i.e., they showed a reduction in cognitive flexibility). The drugs did not alter eye movements *per se*, pointing to a purely cognitive effect. After the injection of a high concentration of the D1R antagonist (10 μg/μL, 3 μL), the impairment in learning and cognitive flexibility lasted for about 1 hour, then the drug started to wash out and overall performance recovered (Figure 2C, D). By contrast, monkeys often stopped working right after, or even during, the injection of a high concentration (10 μg/μL, 3 μL) of the D2R antagonist. The latter reflects either a marked demotivation or severe cognitive deficiencies. In the few remaining sessions when the monkeys did not stop working, learning was moderately impaired, although less than after the D1R blocker, and inflexibility markedly increased (Figure 2C, D). A much lower concentration (0.3 μg/μL, 3 μL) of the D2R antagonist did not prompt the animals to stop working but produced learning deficits and decreases in flexibility. Thus, PFC D2R may play a larger role in motivation than D1R.

The distribution of the sites in the PFC that produced alterations in behavior were different for the two antagonists. The D1R blocker caused learning deficits when injected in the ventrolateral aspect of the PFC (vlPFC), whereas the sites unaffected were mainly in the dorsolateral region (dlPFC). This anatomical dissociation was not observed after injection of the D2R antagonist; the sites producing impairment were equally distributed in both regions of the PFC. However, a key issue when comparing the range of actions following infusions D1R vs. D2R antagonists into different PFC regions is how far the compounds travel. D2R antagonists are often more lipophilic than D1R antagonists (Fleminger et al., 1983), so it is plausible that the D2R antagonist was able to act at either dlPFC or vlPFC sites because it is more lipophilic and can travel farther. Furthermore, when comparing learning rates, we found that blocking D1R induced more severe learning impairment than blocking D2R, even when we injected a very high concentration of the D2R antagonist (Figure 2C). Conversely, blocking D2R led to more inflexible errors (two or more consecutive incorrect responses after the presentation of the same cue), suggesting that D2R are more involved than D1R in this simple type of cognitive flexibility (Figure 2D). These results are consistent with a reduction of spontaneous flexibility in rats after local injections of D1R and D2R antagonists into the medial PFC (Lanser et al., 2001; Ragozzino, 2002). The complementary roles of D1R and D2R in PFC function -predominant role of D1R in associative learning and D2R in cognitive flexibility- support the hypothesis that D1R activation promotes the stabilization of stimulus-reward behaviors after initial learning of associations, whereas D2R activation destabilizes PFC network states favoring flexible processing to allow exploration of new behavioral strategies (Durstewitz and Seamans, 2008; Durstewitz et al., 2000; Seamans and Yang, 2004; Floresco and Magyar, 2006). Given that learning of novel associations requires initial behavioral flexibility, a fine balance between D1R and D2R activation may be necessary to perform this task. Collectively, our work shows some functional differences in

the way PFC D1R and D2R regulate associative learning and cognitive flexibility, suggesting a cooperative mode of action. In line with the two pathways in the striatum that express D1R and D2R, it is plausible that the two receptors are expressed in separate circuits within the PFC that regulate executive function in different ways. Further investigations will be necessary to resolve this important issue.

We note that we did not assess the actions of D1R and D2R agents in more sophisticated types of cognitive flexibility such as reversal learning (the ability to learn to reverse the association of a previously unrewarded stimulus that becomes rewarded) or attentional-set shifting (shifts of attention from one dimension to another in features of visual stimuli) (Chudasama and Robbins, 2006; Robbins and Arnsten, 2009). Depletion of orbitofrontal DA in marmoset monkeys disrupts attentional-set shifting, increases persistent (error) responding in an extinction paradigm, but does not affect reversal learning, that is largely modulated by serotonin (Roberts et al., 1994; Crofts et al., 2001; Robbins and Roberts, 2007; Clarke et al., 2004, 2005; Walker et al., 2009). Surprisingly, the opposite regulation occurs in the CN; DA, but not serotonin, depletions disrupt reversal learning. These findings provide empirical support for a dissociation between the dopaminergic and serotonergic neuromodulatory systems in corticostriatal circuits (Clarke et al., 2011). Further work will be necessary to fully elucidate the roles of PFC D1R and D2R in the several types of cognitive flexibility.

Noteworthy, blockade of D1R and D2R in the lateral PFC does not influence the performance of highly familiar associations (over one year of training) (Puig and Miller, 2012, 2014) (Figure 2E). From these results we conclude that the impairing effects of the D1R and D2R antagonists on learning are specific (novel and familiar images were interleaved in the same block of trials), and also that DA transmission in the PFC is not essential for the performance of familiar stimulus-response associations. Thus, PFC DA may be crucial for the early stages of learning, but with extended training DA appears to play a decreasing role. This aligns well with the proposed transition from goal-directed to habit-based instrumental performance, initially encoded by the PFC during learning (associative loop through the BG) and later orchestrated by the sensorimotor BG loop when the associations become habits (see above; Wickens et al., 2007; Graybiel, 2008).

Dopamine Receptors Modulate the Activity of Prefrontal Neurons during Learning and Memory

We examined how DA affects neuronal activity of prefrontal neurons in monkeys trained to learn new associations between visual cues and a saccade to the right or left. We recorded local field potentials as well as spiking activity from up to 15 electrodes in the lateral PFC while pharmacologically blocking D1R or D2R (Puig and Miller, 2012, 2014). Typically, the spiking activity of 10–40 isolated neurons was recorded simultaneously in each session. Around 30% of these randomly selected neurons exhibited increases in neural information about the cue-saccade associations that paralleled the monkeys' associative learning. There was a trial-by-trial increase in difference in spiking rate between the preferred and non-preferred saccade directions (neural selectivity) (Figure 1). These learning-related changes in activity were consistent across blocks of trials, where different novel cues were presented.

So, the pattern of activity of these association-selective neurons contained information about all the novel associations in a session. Also included in the task were two familiar cues that had long-practiced associations with the saccades.

Blocking both D1R and D2R in PFC reduced neural selectivity to novel associations in association-selective neurons compared with baseline (pre-drug) and post-saline trials. This was largely due to an increase in spiking rates for the non-preferred saccade direction (see Figure 3A and B for average effects on neural populations and Figure 3C for representative examples). These findings resemble the decrease in spiking rates for the non-preferred saccade direction that a D1R agonist exerts in monkeys performing a spatial working memory task (Vijayraghavan et al., 2007; Williams and Castner, 2006). Thus, D1R needed for generating and refining the representation of a stimulus in working memory may also be engaged in the refinement of a SR association. This suggests DA may utilize a common cellular pathway to modify neural information during executive function. Moreover, our findings point to a mechanism of action shared by D1R and D2R. That is, DA receptors may sculpt neural selectivity of PFC neurons by decreasing activity to non-preferred directions thus reducing the neural signal-to-noise ratio (Arnsten, 2011). In addition, it is possible that DA release in response to an error further sculpts and refines representations by engaging DA receptors (Arnsten et al., 2012).

An overlapping (~40%) but distinctive population of PFC neurons showed selectivity during performance of the familiar cue associations. D1R and D2R antagonists did not affect this performance, but they did partly reduce neural information, albeit less so than to the novel cue-saccade associations. It may be that the extensive training in the familiar associations resulted in them being encoded in the sensorimotor striatum and thus less dependent on PFC (Wickens et al., 2007; Graybiel, 2008).

Above, we discussed how DA receptor blockade reduced neural selectivity. There was also a change in the overall level of spiking activity that differed between D1R and D2R blockade; D1R and D2R antagonists increased and decreased, respectively, the average spiking rate of task-selective PFC neurons compared with saline controls (Puig and Miller, 2012 and unpublished results; Figure 3D). Interestingly, a similar link can be made for D2R actions during working memory paradigms, where D2R blockade markedly reduces Response cell firing (Wang et al., 2004). Parallel reductions in neuronal firing during associative learning could lead to the immediate deficits in task performance reported here. The D1R antagonist also generated bursts of action potentials that occurred synchronously in many cells, resulting in an elevated spike-to-spike coherence. Next, we will discuss the implications of this.

Dopamine Receptors Modulate the Activity of Prefrontal Neural Networks during Learning and Memory

Synchronous oscillatory activity across many neurons generates “brain waves” that can be detected via EEGs on the scalp or intra-cerebrally via local field potential (LFP) signals. Specific oscillatory rhythms are correlated with specific behaviors (see for review Engel et al., 2001) and may provide a means for regulating neural communication (Buzsaki, 2004).

This may be especially important for executive brain functions that require coordination of long-range networks across the brain (Buzsaki et al., 2013; Miller and Buschman, 2013).

In rodents learning new rules, oscillatory signals of fronto-hippocampal networks are modulated by DA (Costa, 2011; Benchenane et al., 2010, 2011). Specifically, coherence in theta oscillations (5–10 Hz) between the hippocampus and the medial PFC increases with learning, and this is mimicked in anesthetized rats with local injections of DA in the PFC (Benchenane et al., 2010, 2011; Jones and Wilson, 2005). Moreover, DA increases the temporal precision of interneuronal firing, favoring a more reliable GABAergic inhibition of pyramidal networks during cognitive information processing (Tierney et al., 2008; Benchenane et al., 2010).

We found that as monkeys learned cue-saccade associations, there was an increase in oscillations in the alpha (8–14 Hz) and beta (14–30 Hz) bands (Puig and Miller, 2012, 2014) (Figure 4). Beta rhythms may facilitate long-range communication, contribute to working memory, improve neural signal-to-noise ratio, and help form new neuronal ensembles (Parnaudeau et al., 2013; Gaillard et al., 2009; Kopell et al., 2011; Rubino et al., 2006; Buschman et al., 2012; Antzoulatos and Miller, 2014). Alpha rhythms, on the other hand, may play a role in attention, by helping to suppress unattended information (Bonnefond and Jensen, 2012; Buschman et al., 2012; Jensen et al., 2002). During the learning impairment produced by blocking PFC D1R we observed an aberrant boost in alpha and beta oscillations, that were markedly exaggerated compared with the oscillations observed during normal learning (Figure 4). We also detected enhanced spike hypersynchronization (spike-to-spike coherence), reflected as sharp seizure-like deflections in the LFP signals, never observed during normal learning either. We hypothesize that D1R-related increase in cortical excitability and synchronization could originate from the actions of D1R on NMDA-mediated glutamatergic transmission (Castner and Williams, 2007). Conversely, D2R blockade has less of an influence on PFC rhythms. It increased the power of alpha, but not beta, oscillations and spike hypersynchronization was never observed. This may be due to a combination of two factors. First, blockade of D2R reduced overall spiking activity of PFC neurons, preventing hypersynchronization; and second, D2R are expressed by selective subpopulations of layer V neurons and are not as broadly expressed as D1R in primate cortex (see above). Consistent with our results, blockade of D2R in humans alters alpha oscillations in frontal cortex (Wacker et al., 2013).

Analyses of the frequency-dependent oscillations of the population neural signals in CN and PFC during category learning (Antzoulatos and Miller, 2014), revealed that, during the learning of the categories there was enhanced synchronization between the PFC and CN beta rhythms only after the animal had made its decision, and was ready to report the category membership of the tested stimulus. However, after the learning of these new categories was complete, and the animal's behavior had reached a stable level of proficient categorization performance, presentation of each new category exemplar led to category-selective synchronization between PFC-CN pairs of sites, indicating that learning had led to the formation of functional circuits specific to the category. Interestingly, the effects of learning on synchronized oscillations were only observed between PFC and CN, not within either area. Additionally, during the SR learning stage of the experiment, oscillations in PFC and

CN were more synchronized during the error than the correct trials. This result, along with the observed increase in oscillations during the learning impairment produced by the DA receptor antagonists (Puig and Miller, 2012, 2014) indicate that synchronized activity does not always function to facilitate the information transfer between areas and to improve performance. Apart from the generalized synchrony that defines epileptic seizures, strongly synchronized oscillations (between the beta rhythms in frontal cortex and BG) have also been correlated with Parkinson's disease (Hammond et al., 2007). Clearly, our understanding of the role of synchronized oscillations is still in its infancy, and further research will help identify the conditions under which they facilitate or impede information processing and communication between areas.

Conclusions

Dopamine transmission in the lateral PFC may be relevant for learning-related cognitive functions. First, DA neurons in the SNc and the VTA project to the lateral PFC, where neural activity increases robustly during tasks that require new learning and motivation. It is likely that DA neurons encoding motivational salience are responsible for this, since subpopulations of neurons in the lateral PFC are excited by both rewarding and aversive visual cues. Moreover, research conducted in our laboratory has recently shown that PFC D1R and D2R play complementary roles in associative learning, cognitive flexibility, and motivation, but do not contribute to the performance of familiar associations. Thus, PFC DA may be crucial for the early stages of learning, but other structures (e.g., the striatum) take over when cognitive demands decrease and the associations become habits. Importantly, D1R and D2R needed for generating and refining the representation of a stimulus in working memory may also be engaged in the refinement of an association, pointing to a common cellular mechanism of action of the DAergic system in the lateral PFC during executive function.

The technical advances developed in the field in the last decade have allowed to tackle difficult questions such as the involvement of DA in the neural mechanisms of learning and memory. However, recent findings on the sophisticated anatomy of DAergic circuits in the midbrain underlying reward and aversion suggest that this endeavor might prove to be more challenging than anticipated. Whether or not the two populations of PFC neurons expressing D1R or D2R contribute to different aspects of learning and memory will need to be determined. Our results show that blocking both PFC D1R and D2R results in learning deficits and decreases in learning-related neural information. We also found that DA regulates oscillatory activity in the PFC. Blocking D1R increased global excitability and synchronization of neurons and increased alpha and beta oscillations. By contrast, blocking D2R increased alpha, but not beta, oscillations and reduced neuronal excitability. Collectively, our work shows that prefrontal D1R and D2R modulate associative learning in a cooperative manner. We hope our findings will provide new insights into the role of PFC DA transmission in associative learning and memory.

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Highlights

- Prefrontal D1R and D2R modulate associative learning and cognitive flexibility
- Prefrontal D1R and D2R modulate learning-related neural information
- Blocking D1R increases alpha and beta oscillations and neuron excitability
- Blocking D2R increases alpha oscillations and reduces neuron excitability
- Prefrontal D1R and D2R modulate learning in a cooperative manner

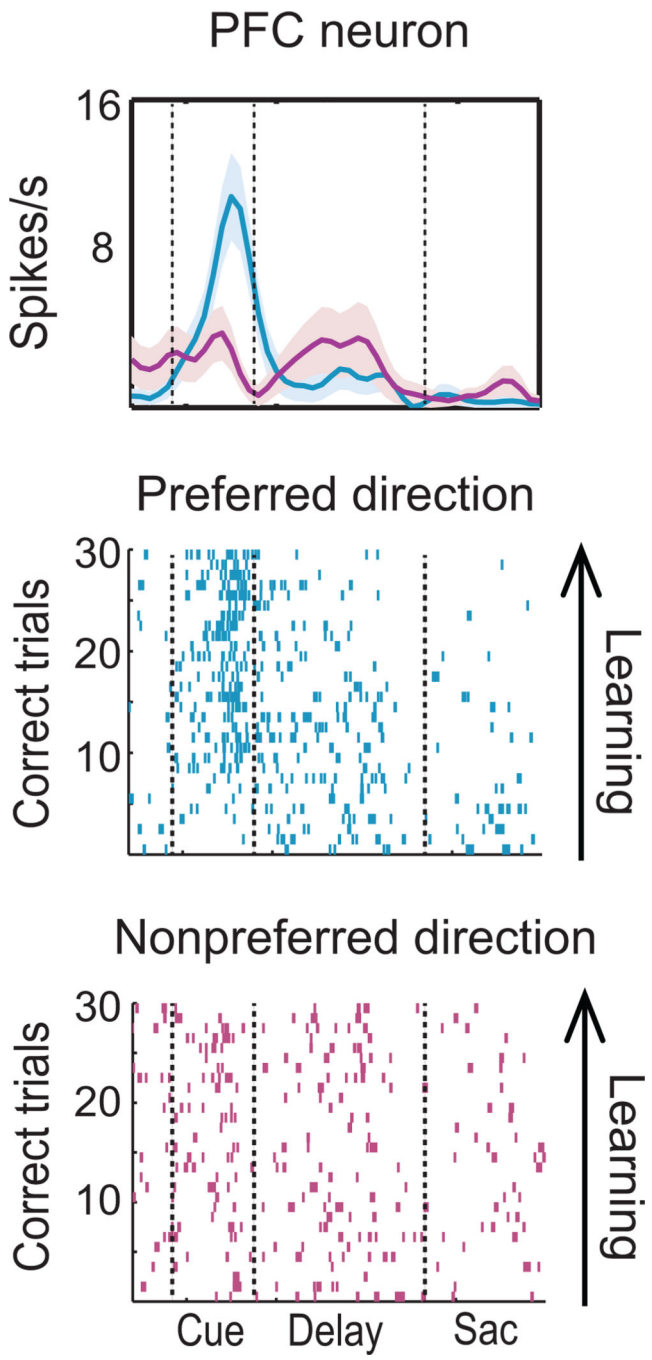

Figure 1.

Learning-related changes in spiking activity of an example neuron recorded in the lateral PFC of a monkey. The monkey learned by trial and error the correct association between a visual cue presented at the center of the screen and a saccade to a right or left target. Shown are raster plots of the spiking activity in correct trials for the preferred and nonpreferred saccade direction and the corresponding quantification. With learning, as the monkey was increasingly able to predict the forthcoming saccade that would yield a reward, the neuron built up saccade direction selectivity during the cue epoch of the trial.

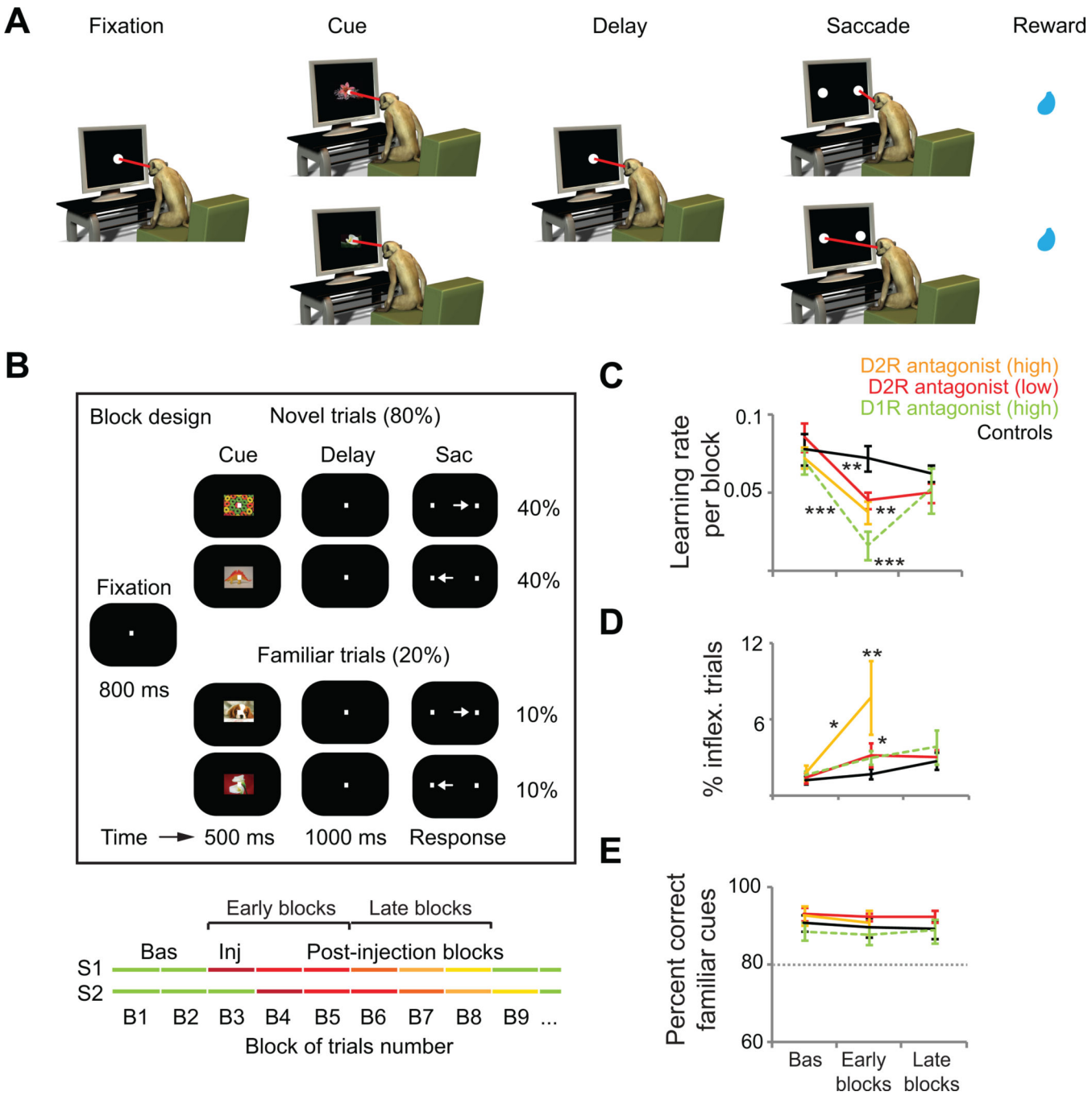

Figure 2.

Blocking D1R and D2R in the PFC impairs learning of new associations and cognitive flexibility, but not memory of familiar associations. A) Basic scheme of the delayed associative learning and memory task. Briefly, monkeys fixated to start trial; a cue object was presented at the center of the screen followed by a brief memory delay and presentation of two target dots. Saccade to the target associated with the cue was rewarded with juice drops. B) Detailed information about the blocking of trials and the pharmacology experiments. Trials were blocked in pairs of novel cues (novel trials; 80% of trials), and

pairs of familiar cues (familiar trials; 20% of trials). When performance of novel trials reached the learning criteria (80% correct and 30 correct trials per novel cue), novel cues were replaced and a new block started. Monkeys first completed several Baseline blocks (Bas; first green lines). Then, 3 μl of either the D1R antagonist SCH23390 (30 μg, high concentration) or the D2R antagonist eticlopride (30 μg or 1 μg, high and low concentrations, respectively) were pressure-injected in the left lateral PFC (Inj; injection block). The performance during postinjection blocks was compared to baseline blocks and saline controls. Drugs were injected after different numbers of baseline blocks in different sessions (S1-S2) to account for any confounds generated by a systematic behavior of the monkeys. We classified blocks as baseline, 'early' (injection block and first two postinjection blocks), or 'late' (postinjection blocks 3 to 5). C) Average learning rates across sessions during the baseline, early, and late blocks. Learning rates decreased significantly after the injection of both SCH23390 and eticlopride compared to baseline and post-saline blocks, but less after eticlopride than after SCH23390. D) Average percent of perseverative errors (consecutive error trials of the same cue) during baseline, early, and late blocks. Perseverative errors increased significantly after the injection of both SCH23390 and eticlopride compared to baseline and post-saline blocks, with the high concentration of the D2R antagonist having the maximum effect. (E) Average percent correct of familiar trials. Dashed line depicts the 80% threshold used as learning criterion. None of the treatments affected the performance of familiar associations. Two-way ANOVA for treatment and block as factors. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$, Tukey's least significant difference posthoc test. Shown are the mean and SEM. Modified from Puig and Miller 2012, 2014.

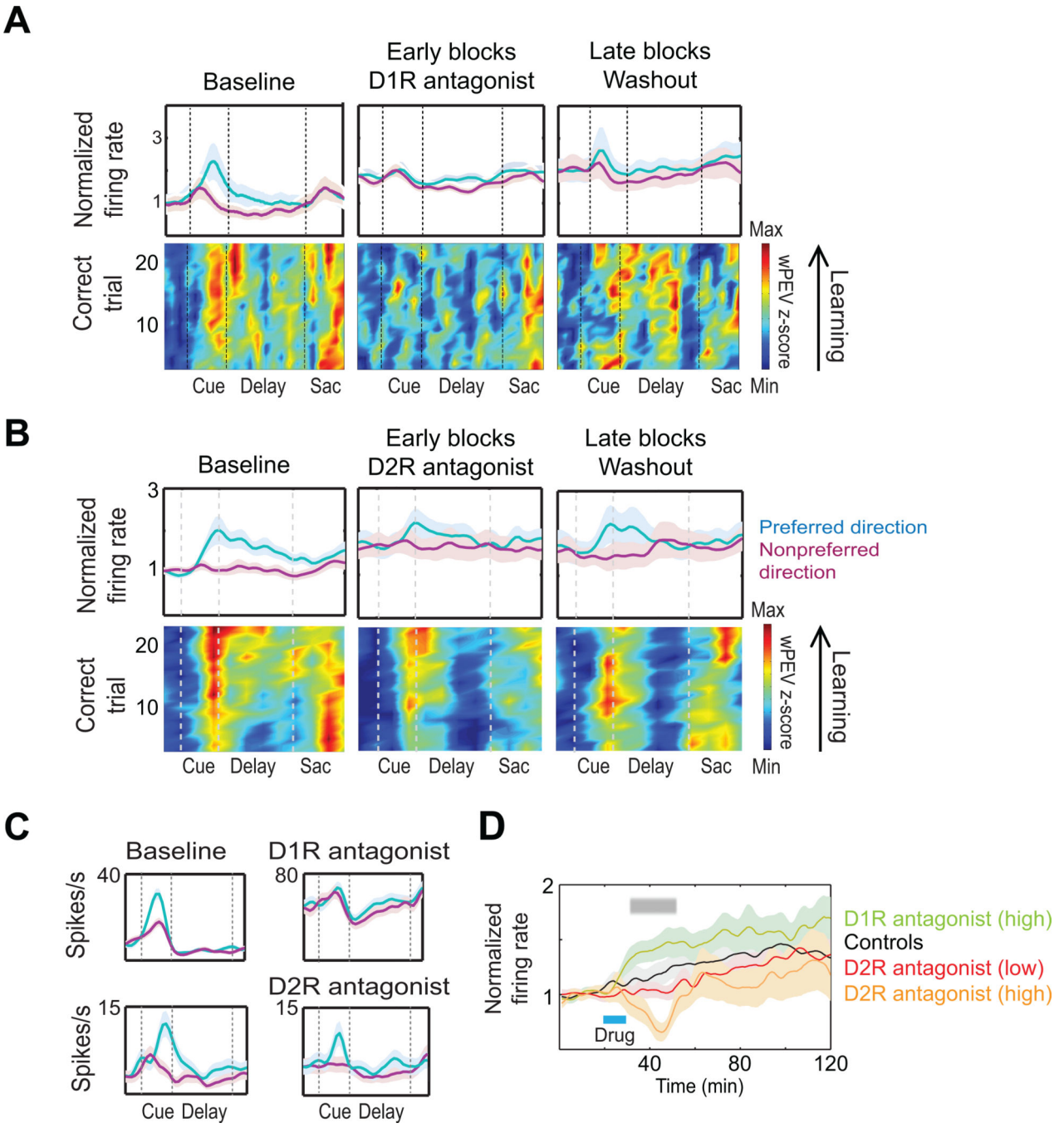

Figure 3.

Neural selectivity is modulated by D1R and D2R during associative learning in the PFC. A and B) Normalized firing rate of neurons selective to novel associations before and after the microinjection of 30 μg of SCH23390 (D1R antagonist) or 1 μg of eticlopride (D2R antagonist). Spiking activity was normalized by the mean firing rate during the fixation period (300 ms before cue presentation) in baseline blocks. Also shown is a colormap of the strength in direction selectivity (proportion of explainable variance by direction factor ωPEV normalized with a z-score, all correct trials per cue) as monkeys learned the

associations. Both antagonists reduced neural selectivity in PFC neurons, but the effect of the D1R antagonist was more pronounced. C) Two representative example neurons depicting the effects of D1R and D2R antagonists on neural selectivity. D) Average normalized firing rates of neurons selective to novel associations. Shaded area indicates significantly higher and lower firing rates relative to saline after 30 μg of SCH23390 and 30 μg of eticlopride, respectively (Wilcoxon test, $p < 0.05$). Saline, 81 neurons; SCH23390, 78 neurons; eticlopride (30 μg), 31 neurons; eticlopride (1 μg), 69 neurons. Modified from Puig and Miller 2012, 2014.

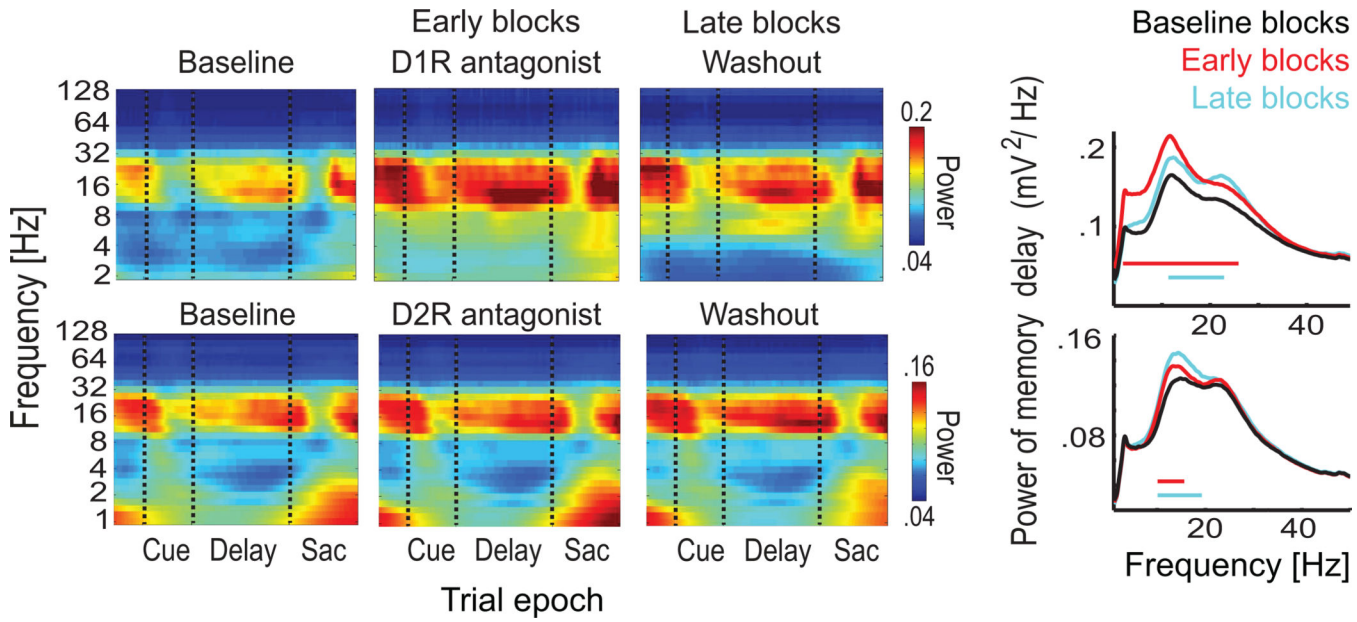

Figure 4.

Blocking D1R and D2R differently affects the power of alpha (8–14 Hz) and beta (14–30 Hz) oscillations in the PFC. Time-frequency representation of the average LFP power using wavelets for correct novel trials during baseline, early, and late blocks, and corresponding power spectra of the memory delay. In the delayed associative learning and memory task prominent alpha and beta oscillations are present during the delay epoch of the trial. Blocking PFC D1R increased the power of both alpha and beta oscillations, whereas blocking PFC D2R increased the power of alpha oscillations only. Wilcoxon ranked test, $p < 0.05$. Modified from Puig and Miller 2012, 2014.