

Doping the Mind: Dopaminergic Modulation of Prefrontal Cortical Cognition

The Neuroscientist
2016, Vol. 22(6) 593–603
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DOI: 10.1177/1073858415602850
nro.sagepub.com



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Abstract

The prefrontal cortex is the center of cognitive control. Processing in prefrontal cortical circuits enables us to direct attention to behaviorally relevant events; to memorize, structure, and categorize information; and to learn new concepts. The prefrontal cortex receives strong projections from midbrain neurons that use dopamine as a transmitter. In this article, we review the crucial role dopamine plays as a modulator of prefrontal cognitive functions, in the primate brain in particular. Following a summary of the anatomy and physiology of the midbrain dopamine system, we focus on recent studies that investigated dopaminergic effects in prefrontal cortex at the cellular level. We then discuss how unregulated prefrontal dopamine signaling could contribute to major disorders of cognition. The studies highlighted in this review demonstrate the powerful influence dopamine exerts on the mind.

Keywords

prefrontal cortex, cognitive control, neuromodulation, dopamine, nonhuman primate

Introduction

An animal's well-being in its environment depends on its choices and actions. On a daily basis, we encounter two distinct types of situations that require specific actions to ensure desirable outcomes. Some actions are not preceded by elaborate consideration, and their execution is rather automatic, for example, reaching for the light switch in a dark room with the intention of illuminating it. Other situations require us to more carefully assess our options before making a choice: one needs to examine the direction of movement of a two-way escalator before boarding it, depending on whether one desires to go up or down. Unselectively boarding the elevator will not yield a satisfactory outcome in all instances. Here, an executive center of the brain is needed to make an assessment of the current situation and process incoming information to fit internal goals and initiate appropriate motor sequences.

The dorsolateral prefrontal cortex (PFC) is regarded as the center of executive control where afferent sensory information is compared with internal goals to orchestrate behavior (Miller and Cohen 2001). The dorsolateral PFC is the brain region that expanded most during primate evolution with new tissue added to the frontal pole of the brain (Preuss 1995). It sends and receives projections to and from virtually all cortical sensory systems (Barbas 1988; Barbas and Mesulam 1985), motor systems (Bates and Goldman-Rakic 1993), and many subcortical structures

(Cummings 1995). The PFC is the seat of top-down control of behavior. Its activity underlies executive functions such as working memory, selective attention, cognitive flexibility, behavioral inhibition, and rule-based reasoning. Illuminating a dark room, on the other hand, is an example of a more reflexive, bottom-up action subserved by different, mainly subcortical brain structures.

All neuronal systems are subject to neuromodulation. Neuromodulators greatly influence the firing properties of target neurons and massively alter their output (Marder 2012). Multiple subcortical neuromodulatory systems that include dopamine, noradrenaline (norepinephrine), serotonin, and acetylcholine neurons send strong projections to the PFC. Dopamine is traditionally and most frequently studied in the setting of reward and motivation, acting mainly via subcortical structures (Schultz and others 1997). However, in the late 1970s already it was discovered that dopamine is also required for high-level cognitive processes that are generated by the PFC (Brozoski and others 1979). Since then, dopaminergic modulation of prefrontal cortical cognition has been

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studied in increasing detail in rodents, nonhuman primates, and humans.

The goal of this review is to highlight recent neurophysiological evidence that uncovers the contribution of dopamine to PFC functions at the cellular level. After a brief exposition of the anatomical and physiological principles of the dopamine system, emphasis will be placed on dopaminergic modulation of individual executive control processes in the primate brain.

Anatomy of the PFC-Projecting Dopamine System

Dopamine neurons have traditionally been identified by the expression of catecholamine synthesizing enzymes such as tyrosine hydroxylase (TH) (but see Lammel and others, 2015, for the view that the dopamine transporter DAT might be better suited). The total number of dopamine neurons, determined by TH immunostaining, is around 20,000 to 30,000 in mice (Nelson and others 1996), 45,000 in rats (German and Manaye 1993), 110,000 to 220,000 in monkeys (Emborg and others 1998), and 230,000 to 430,000 in humans (Chu and others 2002). TH neuron counts decrease significantly with age.

Depending on their targets, dopaminergic projections from the midbrain can be classified into mesolimbic, mesostriatal, and mesocortical pathways. The origin and targets of mesocortical dopaminergic projections to PFC were found to be quite different in primates and rodents. In primates, two distinct pathways of midbrain dopamine afferents project to different areas of the PFC: the dorsal and lateral midbrain dopamine neurons project to the lateral PFC, whereas the ventral midbrain dopamine neurons project to the medial aspects of the PFC (Fig. 1a). In macaque monkeys, dopaminergic projections to the dorsolateral PFC arise from the dorsal and lateral regions of three midbrain areas, namely, the retrorubral area (RRA; A8), substantia nigra (SNc; A9), and parts of the ventral tegmental area (VTA; A10); the ventromedial regions of the PFC receive projections from the medial parabrachial pigmented nucleus and linear nuclei of the VTA (Williams and Goldman-Rakic 1998). However, in rats, most of the dopaminergic innervation of the PFC comes from the VTA, substantially fewer cells from the SNc, and almost no innervation from the RRA (Deutch and others 1988) (Fig. 1b).

Dopamine fibers innervate both excitatory pyramidal and inhibitory GABAergic cells in PFC, enabling dopamine to play a complex modulatory role during prefrontal cortical processing. At the subcellular level, dopaminergic afferents form so-called synaptic triads with postsynaptic pyramidal neuron spines that receive another, presumably

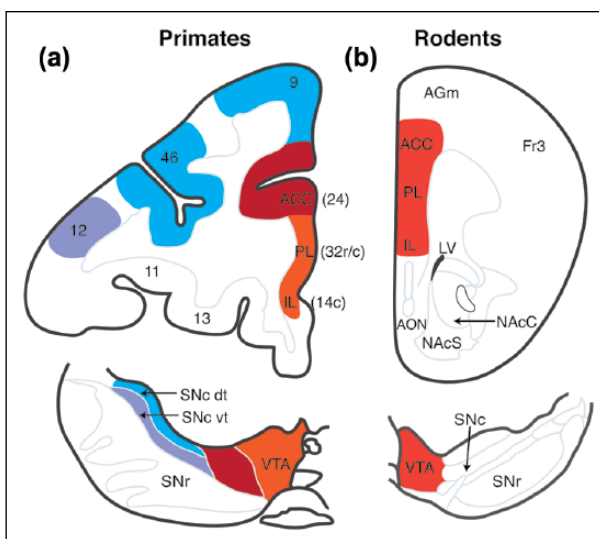


Figure 1. Comparative anatomy of mesoprefrontal dopaminergic projections. (a) In primates, medial regions of the dopaminergic midbrain project to medial regions of the PFC, whereas lateral regions of the midbrain project to lateral regions of the PFC. (b) In rodents, VTA projections predominately target the medial PFC. AGm = medial agranular prefrontal cortex; ACC = anterior cingulate cortex; PL = prelimbic cortex; IL = infralimbic cortex; AON = anterior olfactory nucleus; Fr3 = frontal region 3; NAcC = nucleus accumbens core; NAcS = nucleus accumbens shell; SNc = substantia nigra pars compacta (dt = dorsal tier, vt = ventral tier); SNr = Substantia nigra pars reticulata; VTA = ventral tegmental area; LV = lateral ventricle. Numbers indicate Brodmann areas. Data compiled from Paxinos and Franklin (2012); St Onge and others (2012); Vertes (2003); Williams and Goldman-Rakic (1998).

glutamatergic input (Goldman-Rakic and others 1989) (Fig. 2). Interestingly, dopamine receptors (see Box) are only rarely found at dopamine neuron synapses but more frequently at extrasynaptic sites, possibly receiving dopamine via diffusion in the neuropil (volume transmission) (Smiley and others 1994).

Midbrain dopamine neurons are part of extensive sub-cortico-cortical processing loops and receive strong feedback connections, for example, from neurons in the PFC (Carr and Sesack 2000). Neurons in the rodent PFC project to VTA neurons and the nucleus accumbens, potentially influencing dopamine release along the mesocortical, mesostriatal, and mesolimbic pathway (Kim and others 2015). Interestingly, this subset of PFC neurons synapses onto those VTA neurons, which project to them, but not to the VTA neurons projecting to other brain regions, for example, the nucleus accumbens (Carr and Sesack 2000). Such circuit specifications could allow for highly coordinated information processing that would be required for executive control.

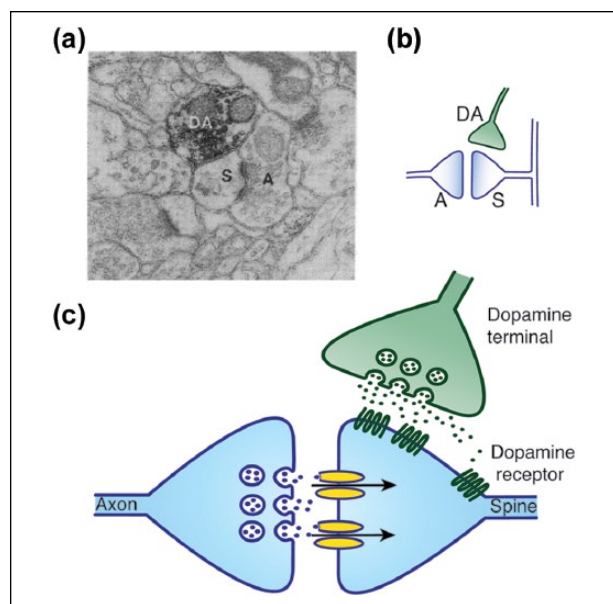


Figure 2. Synaptic triads. (a) Electron micrograph from prefrontal cortex (PFC) showing a dopamine positive axon terminal (DA) making contact with a postsynaptic neuron (S) that receives presynaptic input (A), forming a synaptic triad. (b) Schematic of the synaptic triad. (c) Magnification of the synaptic triad. Cartoon shows a PFC synapse in which the activity of the postsynaptic neuron is modulated by dopamine release and subsequent dopamine receptor activation. Subpanel (a) reproduced with permission from the National Academy of Sciences.

Dopamine Receptors

Dopamine exerts its effects through receptors categorized into two major families: the D1 family, comprising the D₁ and D₅ receptors, and the D2 family, comprising the D₂, D₃, and D₄ receptors. Both D1 and D2 classes of receptors are G protein coupled receptors, which initiate intracellular signaling cascades rather than inducing postsynaptic currents directly (Lachowicz and Sibley 1997; Missale and others 1998; Yang and Seamans 1996). In the PFC, D1Rs are by far the most abundant form of dopamine receptors (Goldman-Rakic and others 1992; Lidow and others 1991); they are widely expressed in supra- and infragranular cortical layers (Lidow and others 1991). D2Rs, in contrast, are mainly confined to cortical layer 5 (Lidow and others 1998). Both pyramidal and GABAergic neurons of the PFC express dopamine receptors, indicating that dopamine modulates excitatory and inhibitory synaptic transmission (Santana and others 2009).

Physiology of Dopamine Neurons

The most widely studied feature of dopamine neuron activity is their time-locked firing of action potentials in close

succession to the presentation of rewarding stimuli. Through their time locked firing, termed “phasic” activity, dopamine neurons are known to communicate a “reward prediction error” that signals the difference between predicted reward and actual reward (reviewed in Schultz 2007). In dopamine neurons in the VTA (area A10), a larger reward than predicted elicits phasic activation, whereas a smaller reward than predicted elicits phasic silencing; a fully predicted reward elicits no response (Schultz and others 1993). The reward prediction error is thought to represent a teaching signal that strengthens the association between a reward and its conditioned predictor. These neurophysiological findings have formed the basis for the large amount of studies investigating dopamine’s role in appetite, motivation, and reward-related learning.

How do dopamine neurons respond when an aversive stimulus is encountered? Matsumoto and colleagues probed into the activity of midbrain dopamine neurons when monkeys were presented conditioned predictors of rewarding or aversive stimuli (Matsumoto and Hikosaka 2009). They found a subset of dopamine neurons in the ventromedial midbrain that were activated at the presentation of the cue predicting liquid reward and inhibited at the presentation of the cue predicting aversive air puffs. This finding is similar to the results of Schultz and colleagues; while reward predictive cues were encoded in the same way in both studies, cues predicting aversive stimuli were represented in a manner similar to reward omission. Interestingly, a distinct subgroup of dopamine neurons in the dorsolateral midbrain was activated at the presentation of cues predictive of both rewarding and aversive stimuli (Matsumoto and Hikosaka 2009). This finding lends support to the idea that some dopamine neurons might communicate predictive information about both positive and negative outcomes. Finally, a third subgroup of dopamine neurons was activated by “free” (i.e., not predicted) liquid reward and air puffs. These neurons might communicate a saliency signal an animal could use to process unexpected stimuli in its environment, regardless of carrying positive or negative value. In sum, different functional subgroups of midbrain dopamine neurons convey both motivational and cognitive salience (Matsumoto and Takada 2013). The medial-to-lateral, “motivational-to-cognitive” gradient in the midbrain is in direct correspondence with the target regions in medial “motivational” and lateral “cognitive” PFC, respectively (see Anatomy section). Dopamine neurons are active in a variety of behaviorally relevant scenarios and transmit a repertoire of signals to PFC that is suited to inform appropriate, goal-directed executive responses.

Dopaminergic Modulation of Prefrontal Executive Functions

A growing body of evidence shows that prefrontal dopamine receptors control several important cognitive behaviors. The

specific role of the two dopamine receptor families in various PFC functions will be discussed in the following sections.

Working Memory

The term working memory is sometimes synonymously used with short-term memory, episodic buffer, or phonological loop (Baddeley 1992, 2000). These terms refer to the type of memory that is required to store information for short time periods (seconds to minutes) in the absence of external stimuli (Jacob and Nieder 2014), for example, a telephone number before writing it down. The neural correlates of a transiently remembered stimulus were first described in the 1970s (Fuster and Alexander 1971; Kubota and Niki 1971). It was discovered that individual neurons in the monkey PFC show persistent activity in the memory period of a delayed response task. While more recent studies have shown that persistent activity and optimal performance in a working memory task require NMDA receptor activation (Wang and others 2013) as well as alpha2 adrenoceptors (Wang and others 2007), it has long been known that prefrontal dopamine is crucial for the maintenance of working memory. In macaque monkeys performing a delayed alternation reaching task, dopamine levels increased specifically in the dorsolateral PFC, not in any other prefrontal region (Watanabe and others 1997). In rhesus monkeys trained to memorize the location of saccade targets (delayed oculomotor response task tapping spatial working memory), depletion of dopamine (Brozoski and others 1979) or blocking of D1Rs (Sawaguchi and Goldman-Rakic 1991) in lateral PFC caused a significant drop in memory performance (other sensory and motor functions remained intact). These behavioral responses have been extensively investigated at the cellular level (Williams and Goldman-Rakic 1995). Single PFC neurons active in the delay period of the oculomotor task showed improved spatial tuning to preferred remembered locations when stimulated with moderate levels of D1R agonists that were applied using micro-iontophoresis (Vijayraghavan and others 2007). As the dosage of D1R agonist increased, spatial tuning deteriorated again (inverted U response profile) (Vijayraghavan and others 2007). Working memory is also sensitive to overall states of arousal of an animal; high fatigue and stress have been demonstrated to reduce working memory performance. For example, chronically stressed rats display an impairment of spatial working memory, which is rescued by infusions of the D₁R agonist SKF81297 into the PFC; pretreatment with SCH23390, a D1R (D₁R and D₅R) antagonist, blocks the rescue of spatial working memory by SKF81297 (Mizoguchi and others 2000). In contrast, D2Rs are not associated with memory performance per se, but rather with response-related motor functions in the studied tasks (Wang and others 2004).

Given the strong evidence for the crucial role of D1Rs during working memory, it is important to reiterate that DA neurons are generally not persistently active, but fire phasic bursts of action potentials (Schultz and others 1993). In vitro studies have identified a potential cellular mechanism of short-lived persistent activity in prefrontal pyramidal neurons that is dependent on metabotropic glutamate receptor 5 (mGluR5) activation and modulated by D1Rs (Sidiropoulou and others 2009).

Visual Processing and Attention

Much of what is known about attentional processes comes from monkey studies of visual attention. Attention can be thought of as the allocation of mental resources to specific stimuli relevant to internal goals while ignoring nonrelevant or less relevant stimuli (Baluch and Itti 2011). Enhanced visual responses to task-relevant stimuli are observed in the visual cortex when retinotopically corresponding regions in the frontal eye field (FEF), a region of the PFC, are stimulated (Moore and Armstrong 2003). Furthermore, suppression of responses to task-irrelevant stimuli is observed when the FEF is stimulated at the same regions. These findings provide direct evidence for prefrontal enhancement of visual cortical signals and make a strong case for PFC's role in top down control of visual attention.

Noudoost and colleagues recently explored dopamine's modulatory influence on PFC-guided allocation of visual attention in the macaque brain (Noudoost and Moore 2011). They injected the D1R antagonist SCH23390 into FEF sites that represented the same part of visual space (the "response field") as simultaneously recorded neurons in visual cortex area V4. Monkeys were rewarded for choosing between two saccadic targets, one located within the FEF response field and one in the opposite hemifield. Prefrontal D1R antagonism caused monkeys to saccade more frequently toward FEF response field targets, that is, this part of the visual field had grasped their attention. The authors then examined the cellular responses of V4 neurons to D1R manipulation in FEF. D1R antagonism in the FEF altered the response properties of corresponding V4 neurons in three ways: first, there was an enhancement in the magnitude of responses to visual stimulation; second, the visual responses became more selective to stimulus orientation; third, the visual responses became less variable across trials. That is, these neurons displayed changes that are characteristic effects of visual attention. Injection of a D2R agonist into the FEF produced similar saccadic target selection effects but did not change the response properties of neurons in area V4, arguing that the neuronal changes following attention were generated by superficial layers of PFC (Noudoost and Moore 2011).

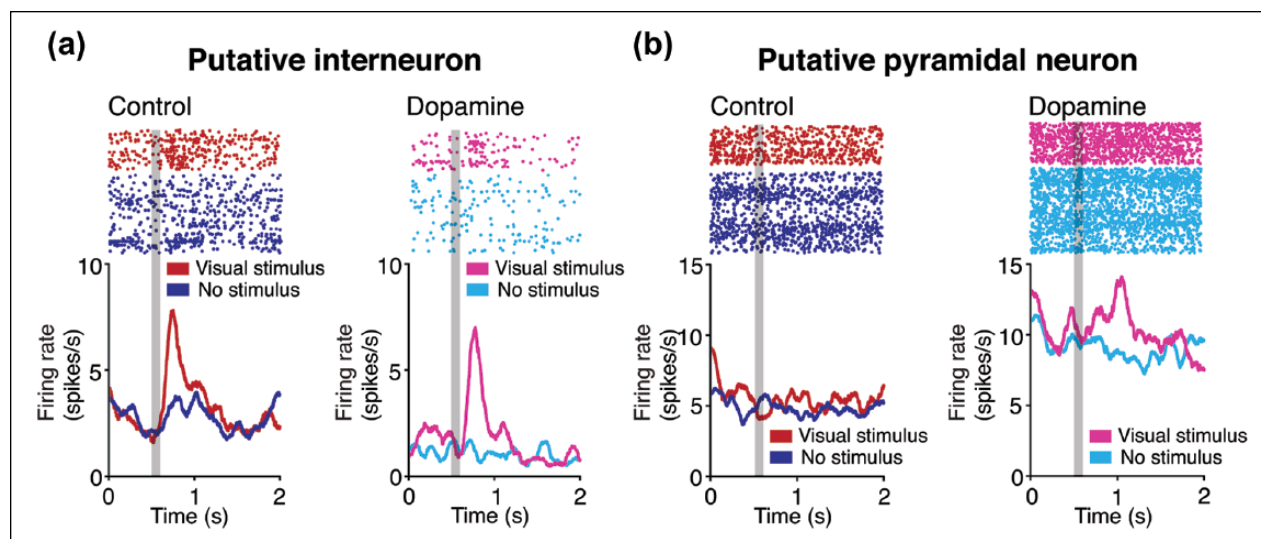


Figure 3. Dopamine modulates prefrontal visual signals in a neuron-class specific manner. Dot raster plots (upper panels; one dot per action potential, one line per trial) and spike frequency histograms (lower panels; smoothed firing rate) show two example visually driven neurons, which are modulated by dopamine. The gray shaded area indicates presentation of stimulus. (a) In a representative putative interneuron, dopamine suppresses neuronal activity compared with the control condition but does not change signal-to-noise ratio (i.e., the coding strength of the visual stimulus vs. baseline/no stimulus). (b) In a representative putative pyramidal neuron, dopamine increases neuronal activity compared with the control condition and significantly improves signal-to-noise ratio. Modified from Jacob and others (2013).

Collectively, this study demonstrates that PFC's long-range top-down control over visual cortical neurons during visual attention is under the influence of dopamine.

Jacob and colleagues recently examined the involvement of dopamine in modulating the activity of PFC neurons receiving visual signals relevant for goal-directed behavior (Jacob and others 2013). Monkeys were trained to report the presence or absence of visual stimuli while single unit recordings were conducted along with micro-iontophoretic application of dopamine to the lateral PFC. Prefrontal dopamine affected two distinct neuronal populations involved in encoding task relevant visual stimuli (Fig. 3). In putative interneurons, dopamine suppressed activity with high temporal precision at unchanged signal-to-noise ratio (Fig. 3a). In putative pyramidal neurons, however, dopamine increased excitability and enhanced signal-to-noise ratio by reducing response variability across trials (Fig. 3b).

Interestingly, putative interneurons and pyramidal cell differed significantly in their visual response latencies, suggesting that they represented two different streams of information processing in PFC (Jacob and others 2013). Putative interneurons had short response latencies, closely matching the discharge of midbrain dopamine neurons at around 100 to 150 ms following stimulus onset, and might serve as a dopamine-modulated gate to sensory inputs reaching the PFC. Putative excitatory neurons, in contrast, fired with much longer latencies. In these neurons, dopamine might strengthen the representation of visual signals

to initiate appropriate downstream actions in response to changes in the sensory environment.

Associative Learning and Cognitive Flexibility

Associative learning is an iterative process by which a link is established between a particular stimulus and a response. Conditioned visuomotor tasks have been used as a model to study learned stimulus-response associations; a typical visuomotor task would involve a protocol where monkeys are rewarded if they saccade to a particular spot contingent on the identity of the visual cue.

Lesions of the PFC significantly impair behavioral performance on visuomotor association tasks (Petrides 1982). To determine whether prefrontal dopamine is involved in forming stimulus-response associations, Puig and colleagues injected the D1R antagonist SCH23390 into the lateral PFC of monkeys learning to associate colored visual cues with an eye movement to the left or to the right (Puig and Miller 2012) (Fig. 4a). Behavioral results showed that the animals learned significantly slower and did not reach peak performance after blocking D1Rs in PFC (Fig. 4b). Performance in trials with previously acquired, familiar associations was not affected, suggesting that D1Rs contribute to learning of novel cues, but not to the recall of already "crystallized" memories. The behavioral changes were accompanied by corresponding changes in the activity of individual prefrontal neurons. Direction selectivity (i.e., the difference in firing

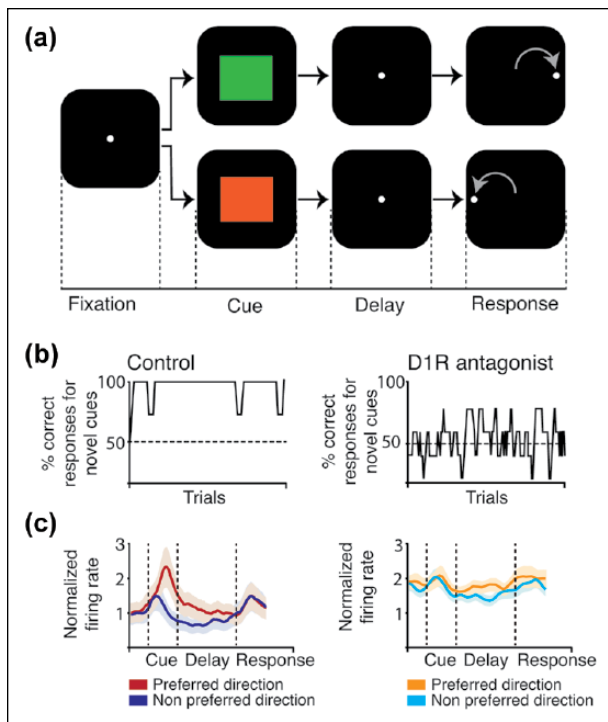


Figure 4. D1Rs are required for associative learning. (a) Schematic showing an association task where monkeys were trained to make a saccade to the left or right depending on the identity of a colored cue. (b) Injection of a D1R antagonist into the lateral PFC causes a decrease in performance during learning of novel cues compared with the control condition (right and left panels, respectively). (c) The D1R antagonist inhibits the development of direction-selective neuronal activity (i.e., the difference in firing rates between preferred vs. nonpreferred saccade directions is reduced). Modified from Puig and others (2012).

rates for preferred vs. nonpreferred saccade directions) failed to develop after injection of the D1R antagonist when the animals attempted to learn new associations (Fig. 4c). Again, neuronal selectivity for familiar stimulus-response mappings was unchanged.

A hallmark of executive functioning is behavioral flexibility, that is, the ability to choose actions appropriate not just to the sensory information at hand but also according to the situation and context in which it is encountered. In the present study, D1R antagonism caused the monkeys to repeatedly make the same erroneous choices (“perseveration”), indicative of cognitive inflexibility (Puig and Miller 2012). Thus, prefrontal D1R activation appears to be required for the animal to flexibly explore different strategies and arrive at the appropriate response. A similar finding had already been made in rats (Ragozzino 2002). Interestingly, perseveration was even more pronounced when D2Rs were blocked with eticlopride, despite the lower concentrations of

D2Rs in PFC compared with D1Rs (Puig and Miller 2015). Learning rates also decreased, but to a lower extent than after blocking D1Rs. In a comprehensive set of experiments, Floresco and colleagues had previously examined the effects of PFC dopamine receptor manipulations in a set shifting paradigm where rats were required to either attend to a visual cue (first day of testing) or ignore it (second day of testing) in order to complete individual tasks (Floresco and others 2006). Similar to the results of Puig and colleagues, blockade of D2Rs dose-dependently impaired the ability of rats to switch strategies in such a set-shifting paradigm and increased perseverative behavior. In sum, the discussed results show that different dopamine receptor subtypes in the PFC influence flexible behaviors in different ways. While D1Rs are crucial for stabilizing new mental representations once effective strategies have been identified, D2Rs could be predominately involved in destabilizing prefrontal networks to allow the animal to explore novel cognitive strategies.

Rule-Based Reasoning

Abstract principles or rules allow behavior to extend beyond specific situations. Rule-based reasoning is a core component of executive control and severely affected after damage to the PFC (Milner 1963). Single neurons in the PFC have been shown to represent abstract rules, irrespective of the sensory modality used to cue the rules (Bongard and Nieder 2010; Wallis and others 2001). A recent study by Ott and coworkers investigated the role of prefrontal dopamine receptors in controlling neuronal representations of rule-guided decision-making (Ott and others 2014). The authors employed a task where monkeys were trained to flexibly apply numerical rules such as “greater than” or “less than” to a varying number of dots (i.e., indicate whether the test stimulus contained more or less dots than the sample stimulus; Fig. 5a). Numerical rules were specified using compound cues comprising both a visual cue and a tactile cue (red/blue ring and liquid/no liquid), so that abstract encoding of the rule could be dissociated from lower level sensory representations. Neurons selective for either of the two numerical rules were identified in the lateral PFC, and their responses to dopamine receptor manipulations were studied using micro-iontophoretic application of D1R and D2R agonists and antagonists.

Both D1R and D2R stimulation resulted in an increase in rule-coding strength (i.e., the difference in firing rates between preferred and nonpreferred rules increased; Fig. 5b) (Ott and others 2014). D1R blockade reversed this effect (Fig. 5c). Interestingly, D1R agonists increased responses to the preferred cue, whereas D2R stimulation suppressed responses to nonpreferred cues. These findings highlight the importance of dopaminergic input to the PFC

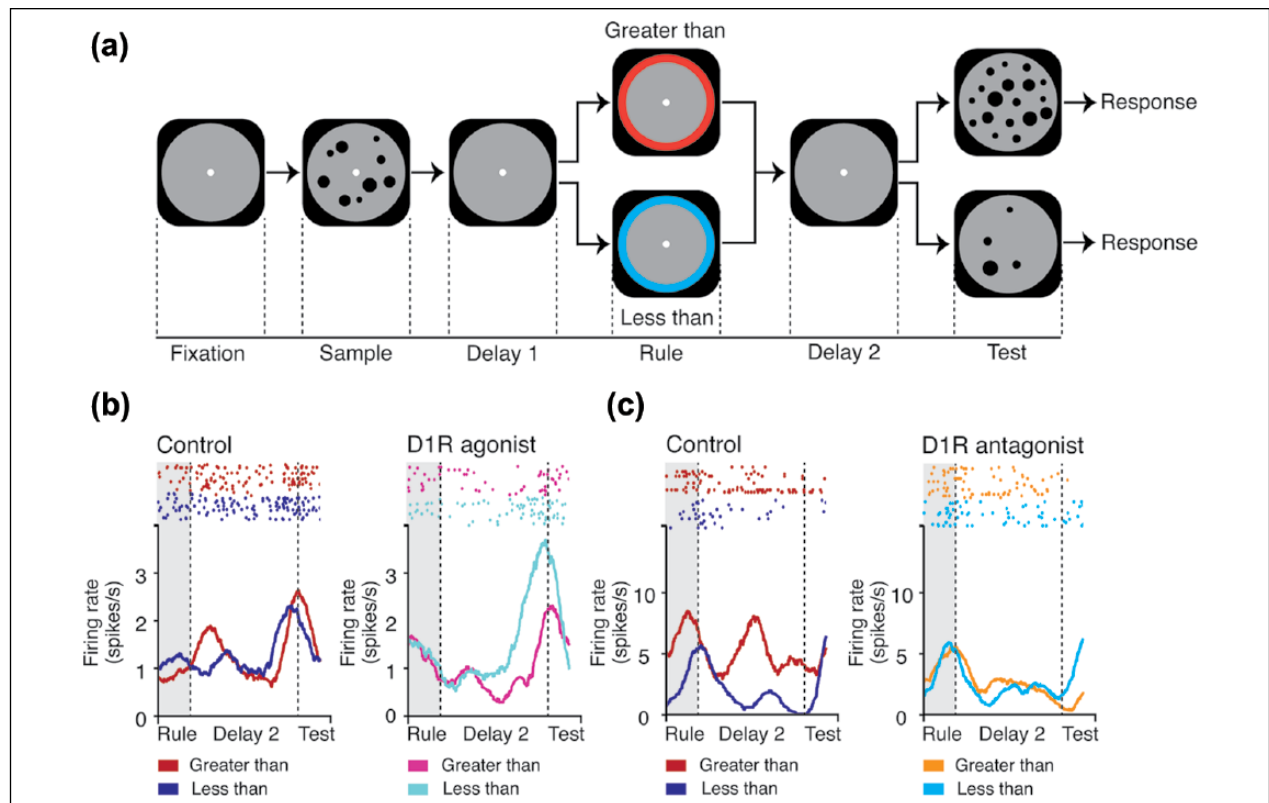


Figure 5. Rule-based decision-making is controlled by prefrontal D1Rs. (a) Schematic of the task protocol. Monkeys were trained to compare the number of dots in a test display to a sample display using numerical rules. The “greater than” rule (top) required monkeys to release a lever if the test display contained a greater number of dots than the sample display, whereas the “less than” rule (bottom) required monkeys to release a lever if the test display contained a smaller number of dots than the sample display. (b) Dot raster plot and spike frequency histogram (as described in Fig. 3) for a single rule-selective neuron that prefers the “less than” rule in control trials (left) and after iontophoretic application of a D1R agonist (right). The D1R agonist improves the neuron’s rule coding strength (i.e., the difference in firing rates between the “less than” and “greater than” rule significantly increases). (c) Same layout as in (b) for a different neuron that prefers the “greater than” rule. Application of a D1R antagonist (right) reduces this neuron’s rule coding strength compared to control trials (left). Modified from Ott and others (2014).

for executive functions and suggest complementary roles for prefrontal D1Rs and D2Rs in enhancing rule coding by sculpting the activity of associated neural substrates.

Dopamine and Frontal Lobe Cognitive Disorders

Given the widespread innervation of many brain regions by dopaminergic fibers, it is not surprising that dopamine signaling has been implicated in a variety of important mental disorders, including addiction, depression, Parkinson’s disease, attention-deficit hyperactivity disorder (ADHD), and schizophrenia.

Disorders of Appetence, Motivation, and Mood

Because the etiology of this group of disorders is closely linked to the dopaminergic subcortical reward circuitry (mesolimbic pathway; nucleus accumbens, striatum), a

comprehensive discussion is beyond the scope of this review. A few cursory remarks are merely intended to direct the interested reader to the relevant literature.

Addiction is the prototypical disorder with major contributions of the dopamine system. Several decades ago, it was discovered that rats eagerly self-stimulated various brain regions electrically such as the septal area and the cingulate cortex (positive reinforcement). Further research showed that these areas contained dopaminergic fibers, and that blocking dopamine receptors abolished the reinforcement effect (all recently reviewed in Nutt and others 2015). These early studies marked the beginning of viewing dopamine as a “pleasure” neurotransmitter and as the central player in stimulant addiction.

Anhedonia, the inability to experience pleasure from normally rewarding stimuli, is a prominent feature in many patients suffering from major depression. Given this cardinal symptom, it is surprising that most attention in the field has focused on hippocampal and frontal

cortical regions, and not on the dopaminergic reward pathways. New evidence is now emerging that structural and functional changes in the mesolimbic dopamine system are associated with depressive symptoms (reviewed in Russo and Nestler 2013). Most notably, recent optogenetic manipulations of dopamine VTA neurons projecting to the nucleus accumbens have shown that this circuit directly contributes to a depression-like phenotype in mice and rats (Chaudhury and others 2013; Tye and others 2013).

Disorders of Higher-Order Cognition

This group of disorders is characterized by prominent dopamine-responsive frontal lobe symptoms, suggesting that the mesocortical dopaminergic pathways that signal cognitive, not motivational, salience are of particular importance (see Physiology section). Further research is clearly warranted, however, to determine the sites and mechanisms of pathology in more detail. For example, disrupted dopamine-sensitive projections to the PFC, for example, from the basal ganglia, could mimic prefrontal pathology (Saunders and others 2015).

ADHD patients suffer from deficits in working memory, inhibitory control, and visual attention, that is, typical prefrontal functions. These functional differences are paralleled by structural anatomical changes in PFC (Seidman and others 2005). Genetic studies have disclosed a plethora of loci that are associated with ADHD, including dopamine-related genes such as the dopamine receptors and the dopamine transporter (Caylak 2012). One of the most frequently voiced arguments for the dopamine-dependence of ADHD is the amelioration of symptoms by the stimulant methylphenidate (Ritalin), which increases synaptic levels of dopamine and other catecholamines. However, the focus on dopamine pathology has been called into question lately because methylphenidate's effect on prefrontal noradrenaline is in fact larger than on dopamine (Berridge and Devilbiss 2011), and because the linkage to dopamine genes is weak and many other susceptibility loci including noradrenaline-, serotonin-, and nervous system development-related genes point to different disease mechanisms (Caylak 2012).

Motor deficits as a consequence of striatal dopamine depletion are of course the dominant sign in Parkinson's disease. However, frontal lobe cognitive dysfunction in these patients is increasingly recognized (Robbins and Cools 2014). Impaired working memory (Mattay and others 2002) and top-down attentional control, where patients' attention is disproportionately captured by salient, yet task-irrelevant stimuli (bottom-up) (Cools and others 2010), have been identified as particular problems resulting from a prefrontal hypodopaminergic state. But

cognitive deficits in Parkinson's disease patients can also arise from medication. Overdosing of dopaminergic drugs has been associated with the development of impulsivity, gambling, addictive behavior, and reduced reinforcement (goal-directed) learning (Robbins and Cools 2014). These latter deficits are likely to involve subcortical structures, for example, the striatum, in addition to a lack of PFC behavioral guidance.

Schizophrenia, the most notable condition in this group, is characterized by positive (psychotic), negative (blunted affect, avolition, motor retardation), and cognitive symptoms (impaired learning and working memory, lack of executive functions). There is ample, long-standing evidence that disrupted dopamine neurotransmission contributes to the generation and maintenance of schizophrenia (so-called dopamine hypothesis of schizophrenia; reviewed in Howes and Kapur 2009). Present hypotheses postulate striatal D2R overstimulation and a concurrent lack of D1R tone in prefrontal regions as important factors (Winterer and Weinberger 2004).

The strongest evidence for the involvement of dopamine in schizophrenia comes from early studies that identified D2Rs as the main target of antipsychotic drugs used to treat positive symptoms (Seeman and Lee 1975). The antipsychotic effectiveness of these agents is correlated with their ability to block D2Rs. Psychosis is believed to originate mainly in the striatum where dopamine neurotransmission via D2Rs is increased, particularly in the dorsal caudate (reviewed in Seeman 2011). Recent data have also revealed a major contribution of extrastriatal thalamic D2Rs to the generation of psychotic symptoms (Chun and others 2014). One of the most influential theoretical concepts in schizophrenia research is the idea of overshooting, "aberrant" salience (Fletcher and Frith 2009; Kapur 2003), whereby an excess of dopamine could make it impossible to suppress irrelevant and interfering sensory input, resulting in hallucinations, delusions, and intrusions of thought. Experimental data to confirm this interesting hypothesis are still lacking, however.

Functional hypofrontality is another frequent finding in schizophrenia (Mueser and McGurk 2004). Consistent with this notion, cognitive symptoms rely heavily, but not exclusively, on the PFC (Eisenberg and Berman 2010). Data on prefrontal D1Rs in schizophrenia patients are inconsistent; positron emission tomography studies have reported both decreased (Okubo and others 1997) as well as increased levels (Abi-Dargham and others 2002; Abi-Dargham and others 2012). Up-regulation of D1Rs could indicate a compensatory mechanism to counteract cortical D1R hypostimulation. Computational models suggest that reduced D1R activity increases noise in the neuronal code and destabilizes prefrontal mental representations (Rolls and others 2008). Jacob and colleagues recently

provided the first experimental data that dopamine indeed controls cortical noise levels in vivo (Jacob and others 2013). Despite the evidence for prefrontal D1R involvement, the administration of D1R agonists to alleviate cognitive symptoms has not met with significant success. Potential reasons are the narrow U-shaped response curve, which might quickly lead to side effects, and the lack of pharmacologically specific agents.

Finally, it is important to appreciate that cortical and striatal dopaminergic dysfunction are linked. For example, prefrontal cortical dopamine activity exerts negative feedback on the midbrain: reduced PFC dopaminergic neurotransmission results in striatal dopamine excess in nonhuman primate animal models (Roberts and others 1994) and schizophrenia patients (Meyer-Lindenberg and others 2002). Several functional imaging studies also emphasize the disruption of distributed neuronal circuits rather than a single brain region in psychotic disorders. This functional interplay will pose additional challenges to better understanding the complex etiology of schizophrenia.

Concluding Remarks

Here, we have summarized the known roles of dopamine and its receptor subtypes in shaping PFC-dependent processes. Several lines of evidence clearly show that dopamine exerts a significant influence on prefrontal cognitive control functions. Due to its extensive midbrain dopaminergic innervation, we speculate that most, if not all, PFC functions could be modulated by dopamine. What is needed now is a significant step forward toward investigating the modulatory mechanisms in more detail at the cellular level. With the advent of techniques to manipulate neuronal activity in genetically defined cell types and with high temporal precision in subjects performing challenging cognitive tasks, it will be possible to develop a deeper understanding of dopamine's role beyond reward and motivation. These experiments will help us unravel its function in a much broader context, namely, in how we perceive, interpret, and respond to changes in our sensory environment. It is this knowledge that will ultimately propel our ability to categorize and treat neuropsychiatric disorders forward.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Deutsche Forschungsgemeinschaft (JA 1999/1-1); the Berlin Institute of Health (BIH TRG4); and

the Bundesministerium für Bildung und Forschung (e:Med "PsychoSys").

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