

Feature Review

Dopamine and Cognitive Control in Prefrontal Cortex

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Cognitive control, the ability to orchestrate behavior in accord with our goals, depends on the prefrontal cortex. These cognitive functions are heavily influenced by the neuromodulator dopamine. We review here recent insights exploring the influence of dopamine on neuronal response properties in prefrontal cortex (PFC) during ongoing behaviors in primates. This review suggests three major computational roles of dopamine in cognitive control: (i) gating sensory input, (ii) maintaining and manipulating working memory contents, and (iii) relaying motor commands. For each of these roles, we propose a neuronal microcircuit based on known mechanisms of action of dopamine in PFC, which are corroborated by computational network models. This conceptual approach accounts for the various roles of dopamine in prefrontal executive functioning.

Prefrontal Cortex, the Central Executive of the Brain

Humans and other animals can engage in flexible behaviors beyond simple stimulus–response associations. The ability to flexibly adjust behavioral responses to produce goal-directed and intelligent behaviors is commonly referred to as ‘cognitive control’ or **executive control functions** (see [Glossary](#)). The PFC at the anterior pole of the endbrain is crucially involved in functions that enable cognitive control, such as stimulus selection, working memory, **rule switching**, decision making, and others [1]. As the central executive of the brain that operates at the apex of the cortical hierarchy, the PFC receives highly synthesized and abstract sensory information, processes it in the light of previous experiences and current demands, and issues commands to motor-related output structures [2–7] ([Figure 1A](#)).

The simplified processing timecourse in the PFC can be illustrated with a ringing telephone. The ringing sound first needs to be recognized as a relevant stimulus that we might act upon. Against the backdrop of many sources of noise, such as other sounds, inadvertence, or a lack of motivation, the sound needs to be ‘gated’ to allow further processing. In a second step, we must decide what to do with the ringing sound. We ‘maintain’ the sound in working memory and manipulate this information in the context of the situation. For example, when the context is ‘at home’, we feel obliged to answer the telephone call. However, if the context is ‘being guest’, we would refrain from responding. In these two conditions, different stimulus–response associations need to be established in an instance. These conditional associations, or rules, determine the logic of a goal-directed task to enable adaptive flexible behavior. Once the rules of the game are clear, the final step is the selection of an appropriate response by ‘relaying’ our decision to motor structures that issue an action, such as picking up the telephone at home, as opposed to carrying on with our conversation if we are guests. In summary, executive control relies on a successful sequence of gating a behaviorally relevant stimulus, maintaining and integrating mnemonic and contextual information during working memory, and relaying this information to premotor areas preparing a behavioral response.

Highlights

Dopamine enables successful cognitive control in prefrontal cortex.

Dopamine receptors in prefrontal cortex control three key aspects of cognitive control – gating, maintaining, and relaying.

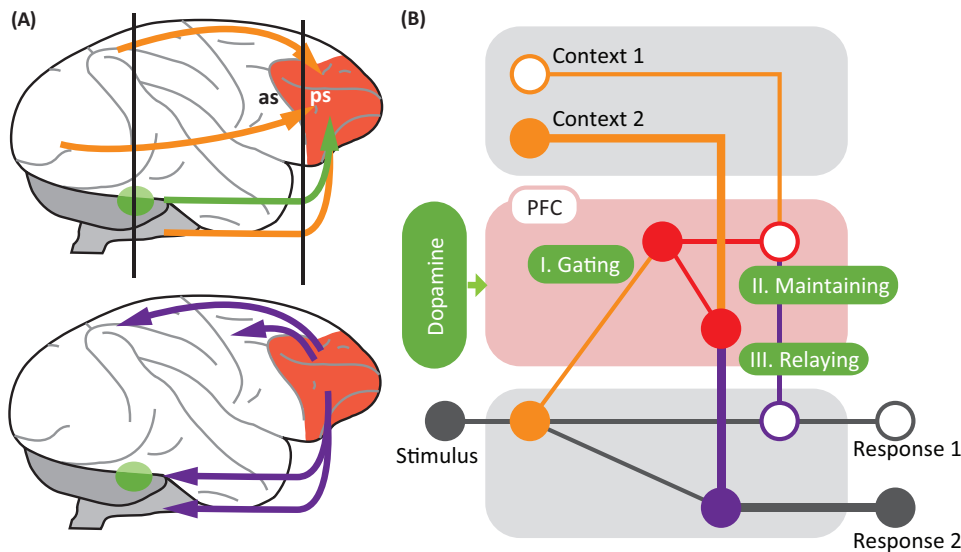
The two major dopamine receptor families, D1R and D2R, assume complementary roles in cognitive control.

Dopamine receptors are differentially integrated in cortical circuit components subserving distinct aspects of cognitive control.

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Figure 1. Dopamine Modulation of Executive Control in Prefrontal Cortex (PFC). (A) PFC (red) receives input from all higher sensory areas as well as from subcortical areas (orange), including neuromodulatory input from the dopaminergic midbrain (green; top), and projects to several cortical and subcortical areas (purple; bottom) [1]. Black lines indicate the approximate location of coronal sections in Figure 2A. (B) Conceptual framework for executive functions in PFC. Behaviorally relevant sensory information and contextual information (orange) are gated in PFC (red box), activating PFC neuron populations (circles) which maintain relevant information in working memory and relay choice signals to downstream target areas preparing motor commands (purple). This model conceptualizes how different context cues can bias the selection of stimulus–response associations towards a goal [8,9]. We review how prefrontal dopamine (green) enables successful execution of all three computations. Abbreviations: as, arcuate sulcus; ps, principal sulcus.

The working of the PFC has been conceptualized in an influential neuronal framework [8,9]. In this framework (Figure 1B), distinct populations of PFC neurons represent the sensation and memorization of sensory stimuli. This information is processed according to different contexts as represented by populations of PFC neurons that encode rules or other goal-relevant information. Because rule-coding neurons are connected to sensory and working-memory neurons, both populations together can bias the selection of a particular action towards a goal by activating appropriate motor responses. In simplified terms, the timecourse of processing in the PFC can be grasped along a threefold processing trajectory: sensory input, memorization and manipulation, and motor output.

Dopamine in the PFC

Processing in the PFC, however, is by no means self-contained. If and how information is passed on from one functional group of PFC neurons to the next is under the crucial influence of the neuromodulatory messenger substance **dopamine**. The neuromodulator dopamine is synthesized by dedicated neurons in the midbrain that send their axons to many brain regions including the PFC [10,11]. When these neurons fire, dopamine is broadly released (from varicosities and terminal endings) into the neural tissue to affect many PFC neurons. Thus, in contrast to neurotransmitters that are responsible for direct synaptic transmission of information from a presynaptic to a postsynaptic neuron, dopamine as a neuromodulator enhances or suppresses this synaptic transmission indirectly by influencing synaptic information transmission.

Glossary

Dopamine: a neurotransmitter released by the midbrain dopamine system, a small set of midbrain nuclei exerting widespread neuromodulatory control over brain function.

Executive control functions: a set of cognitive functions enabling goal-directed execution of behavior, such as working memory, allocation of attention, rule following, categorization, and others.

Gain computation: changing the sensitivity of a neuron by a multiplicative factor in the firing rate following an input.

Inhibitory interneuron: a class of local interneurons of different morphology and biochemistry that inhibit other neurons by releasing the neurotransmitter GABA.

Mesocortical dopamine pathway: a projection pathway comprising midbrain dopamine neurons that project to cortical areas including the prefrontal cortex.

Microiontophoresis: a method that is often combined with electrophysiology to apply small amounts of drugs in the direct vicinity of extracellularly recorded neurons by applying small amounts of current.

Neuronal attractor network: a complex dynamical system of neurons connected via synaptic currents that show several stable, or attractor, states. Typical neuronal attractor network models show two attractor states: a spontaneous, low-firing state and an induced, high-firing state, for example during working memory.

Neuropil: dense network of interwoven axons, dendrites, glia cell processes, and a relatively low number of cell bodies.

Oculomotor delayed response

(ODR) task: a classic behavioral task to probe spatial working memory, in which monkeys must remember the spatial location of a visual cue during a memory delay period.

Pyramidal cell: principal excitatory projection neuronal type in the cerebral cortex.

Reward prediction error: the difference between received and predicted reward, a major

Dopamine is essential for cognitive control functions of the PFC. It influences processes such as working memory [12–15], attention [16,17], and flexible behavior [18–20] that depend on the PFC [1]. Midbrain dopamine neurons in the ventral tegmental area (VTA) and the substantia nigra (SN) project to PFC via the **mesocortical dopamine pathway** (Figure 2A), which can be separated into two parallel systems [21]: the first and evolutionarily older system originates from VTA to innervate the anterior cingulate cortex (Brodmann area 24) and medial frontal areas (areas 14 and 32). In addition, primates developed a distinct mesoprefrontal dopamine system originating from dorsolateral and lateral substantia nigra (SN) to project to the evolutionarily novel and granular dorsal and lateral areas of the PFC (areas 12/47, 9/46, and 9) [21–23].

Once released, dopamine binds to five different dopamine receptors, D₁–D₅, which are G protein-coupled receptors that modulate intracellular signaling cascades rather than producing postsynaptic currents directly [24,25]. Based on structural and pharmacological similarities, these receptors fall into two main receptor types, the dopamine D1 receptor family (D1R) with subtypes D₁ and D₅, and the dopamine D2 receptor family (D2R) with subtypes D₂, D₃, and D₄. D1Rs are expressed in all cortical layers in primate PFC and are about 10-fold more abundant than D2Rs [26]. D2Rs, by contrast, have low expression rates in most layers and show highest expression rates in layer V [26–28]. D1Rs and D2Rs are expressed in both **pyramidal cells** and **inhibitory interneurons** [28–32]. Different functional roles of dopamine are to be expected that depend on receptor subtype, cell type, synaptic properties, and interactions with other transmitters [24].

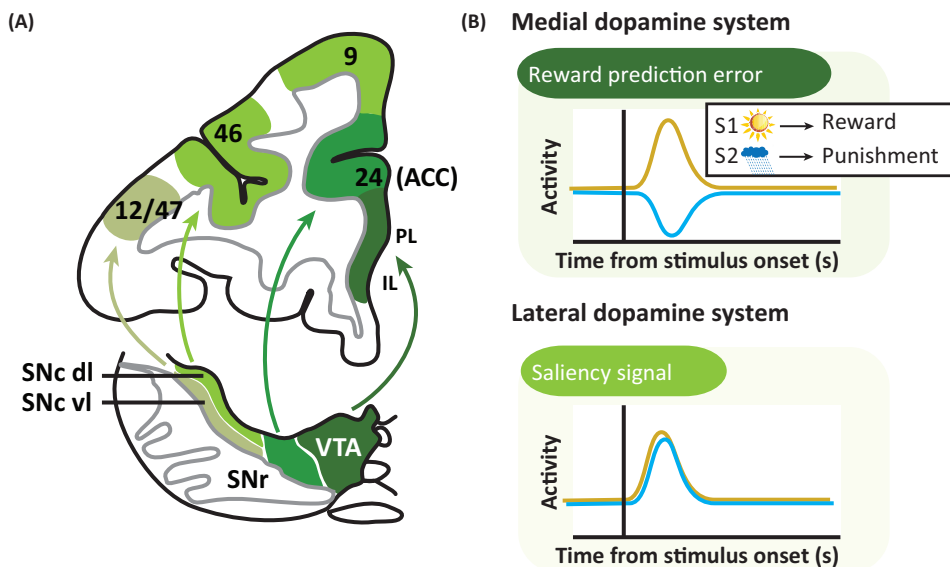
component of reinforcement learning theory.

Rule: conditional associations that determine the logic of a goal-directed task.

Subtraction computation:

changing the sensitivity of a neuron by a subtractive or additive shift in the firing rate following an input.

Synaptic triad: a synaptic structure in which three neurons interact closely with each other. In prefrontal cortex, excitatory synapses form synaptic structures together with dopamine neuron fiber terminals.



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Figure 2. Mesocortical Dopamine System. (A) Mesocortical dopaminergic projections are organized along a mediolateral axis with more lateral dopaminergic neurons (bottom; light green) projecting to lateral and dorsolateral prefrontal cortex (PFC) (top; light green) [21]. (B) Medial dopamine neurons in the midbrain show phasic bursts following reward-predicting cues (S1, symbolized by the 'sun') and suppress activity following punishment-predictive cues (S2, indicated by 'rain'), thus signaling a reward prediction error (top). More lateral dopaminergic neurons, however, convey a saliency signal to PFC [33,50]. Abbreviations: ACC, anterior cingulate cortex; dl, dorsolateral; IL, infralimbic cortex; PL, prefrontal cortex; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; vl, ventrolateral; VTA, ventral tegmental area.

In addition, the origin of dopamine neurons in the midbrain seems to determine dopamine functionality. Dopamine neurons in the VTA or ventromedial SN [33] are known to signal a **reward prediction error** that enables reinforcement learning (Figure 2B, top) [34–42]. The reward prediction error is based on a combination of findings. First, dopamine neurons respond with short, phasic bursts of activity when animals are presented with appetitive stimuli, such as food [43–45]. Second, once the animals have learned to associate a previously irrelevant stimulus with a reward, dopamine neurons shift their phasic activation from the time of reward delivery to the time of presentation of this predictive cue [46]. Third, unexpected omission of reward leads to a suppression of dopamine neurons [47,48].

In contrast to signaling reward prediction error, many dopamine neurons signal the saliency of a stimulus. They are rapidly activated by primary reinforcers that are either rewarding or punishing, or salient and novel stimuli [49–52] (Figure 2B, bottom). Behaviorally relevant stimuli that need to be remembered during working-memory tasks specifically activate the dorsolateral dopamine neurons in SN, and not those located in the ventromedial part of SN [33]. Importantly, dopamine neurons from the dorsolateral SN specifically project to the PFC [21] (Figure 2A), and can therefore modulate PFC networks mediating executive control. Rodent studies suggest that dopamine transients in frontal cortex do not directly mediate reinforcement learning but instead support the recognition of behaviorally relevant stimuli [53,54] necessary for executive control.

In the current review, we capitalize on the finding that dopamine signals in the PFC vary across time [55–57]. In fact, dopamine needs to act at different timescales to influence processing in consecutive stages of a complex delayed response task in which different populations of PFC neurons signal a stimulus, maintain relevant information in working memory to enable memorization and manipulation, and signal a goal-directed motor preparation (Figure 3A, Key Figure). We review how prefrontal dopamine impacts on cognitive control processes at different timescales – from fast and temporally precise gating to maintaining relevant information over longer timescales and invigorating actions. In the subsequent sections we discuss the mechanisms and neuronal microcircuitries for (i) gating, (ii) maintaining/manipulating, and (iii) relaying information that are under the influence of dopamine (summarized in Figure 3B–D).

Dopamine Gates Sensory Signals in PFC

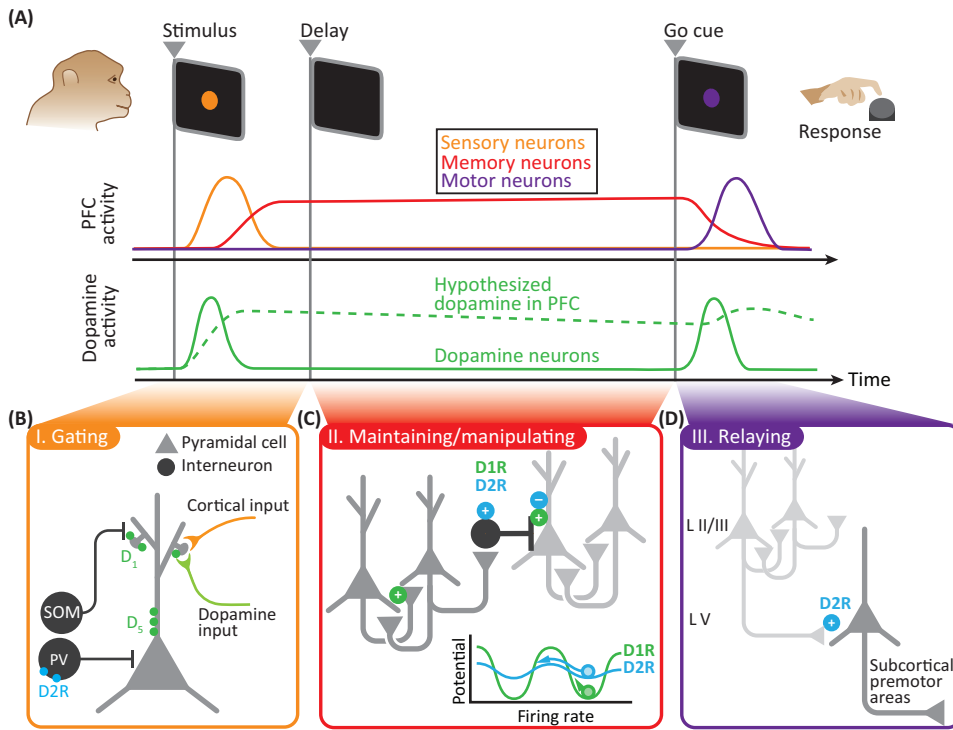
Dopamine Transients Show Characteristics of a Gating Signal

The first component of successful cognitive control is representing relevant sensory stimuli from the environment (Figure 3A). PFC neurons represent basic sensory signals and are tuned, for instance, to motion direction, motion speed, and the luminance of visual stimuli [58–60]. In contrast to neurons in early sensory areas that encode veridical information of the physical stimulus features, the behavioral relevance of stimuli is reflected in PFC neuronal responses [58,61–63]. For example, in visual detection tasks that require a monkey to make a binary decision about the absence or presence of a stimulus, PFC neurons signal the stimulus-present or stimulus-absent percept of the subject rather than the properties of the physical stimulus [3,5,64,65]. The PFC seems to filter, or gate, relevant sensory information for working memory and executive control [7,66–68], albeit by an unknown mechanism.

Salient and behaviorally relevant stimuli activate PFC-projecting dopamine neurons with phasic, short latency responses that quickly release dopamine in PFC. This signal is ideally suited to prompt higher-order areas for the processing of incoming sensory signals [69,70]. Recordings from midbrain dopamine neurons during stimulus detection revealed that dopamine activity reflects perceived stimulus intensity, rather than physical stimulus intensity, because dopamine neurons were only active when the animals successfully detected a stimulus [70]. Remarkably, the latency of

Key Figure

Dopamine Circuit Mechanisms in Prefrontal Executive Control



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Figure 3. (A) Temporal sequence of a delayed response task. (Top row) A typical decision-making task requiring cognitive control comprises a stimulus (orange; left), a subsequent memory delay period (center), and a motor response period (go cue, purple; right). (Middle row) The activity of different populations of prefrontal cortex (PFC) neurons represent all three key variables in the task, such as stimulus-encoding neurons (orange), working memory-encoding neurons (red), and neurons encoding of choice or motor command (purple). Note that encoding schemes might be mixed at the level of single neurons. (Bottom row) Hypothetical dopamine neuron activity and dopamine release in PFC. Midbrain dopamine neurons fire in response to salient stimuli (solid green traces), globally increasing dopamine levels in PFC. During delay periods, dopamine levels in PFC can be prolonged or controlled by local synaptic mechanisms (dashed trace). (B) Proposed dopamine gating circuit. Information about sensory stimuli is routed to PFC via glutamatergic afferents (orange), which form synaptic triads with dopamine fibers (green) in cortical layer II [89]. Dopamine acts on D₁Rs (green) at dendritic spines (predominantly D₁) and shafts (predominantly D₅) [90]. Dopamine could gate incoming information through synaptic modulation of glutamate transmission and control of synaptic input via dendrite-targeting, SOM interneurons (black). Gain modulation of sensory signals might be mediated by soma-targeting, PV-interneurons (black) via D₂Rs (blue). (C) Proposed dopamine maintaining circuit. In a prevalent circuit model for working memory, pyramidal cells (likely in layer II [189,190]) form functional clusters with strong recurrent excitatory connections (grey). Interneurons (black) receive excitatory drive from pyramidal cells and inhibit other pyramidal cells, shaping tuning via lateral inhibition and maintaining an excitation/inhibition balance [143,145,181]. This network exhibits two stable states: a low-firing, spontaneous state and a high-firing, sustained activity state (cf Figure 8A–B). Dopamine controls sustained responses and enhances working-memory stability via D₁Rs, which increase recurrent excitation (NMDA receptors) and inhibitory GABA currents in pyramidal cells (green) [142,145]. D₂Rs, on the other hand, decrease GABA currents in pyramidal cells and control interneuron excitability (blue), which also leads to an increase in sustained responses [99]. PFC networks could switch between a D₁R-dominated state, in which PFC representations are stable and form deep attractor basins (green, inset), and a D₂R-dominated state, in which PFC representations are unstable and fluctuate between attractors (blue) [152,185]. Note, it remains to be resolved if the observed enhancement of sustained activity after D₂R stimulation [99] is congruent with a role for D₂R in destabilizing prefrontal representations. (D) Proposed dopamine relaying circuit. D₂Rs are abundant

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dopamine neuron responses that reflected the choice of the animal matched the latency of neuronal choice signals in frontal cortex, which were delayed relative to visual signals in sensory cortex [71]. This led to the suggestion that dopamine transients in PFC provide a gating signal that allows input to become updated and stored in working memory [72–74]. In support of this hypothesis, human functional imaging activity of midbrain dopaminergic nuclei predicted the responses of context-dependent signals in PFC as well as the behavioral performance of subjects required to make context-dependent decisions (Figure 4A–D) [75]. Results such as this link phasic dopamine signals in the midbrain to PFC signals known to be involved in executive control.

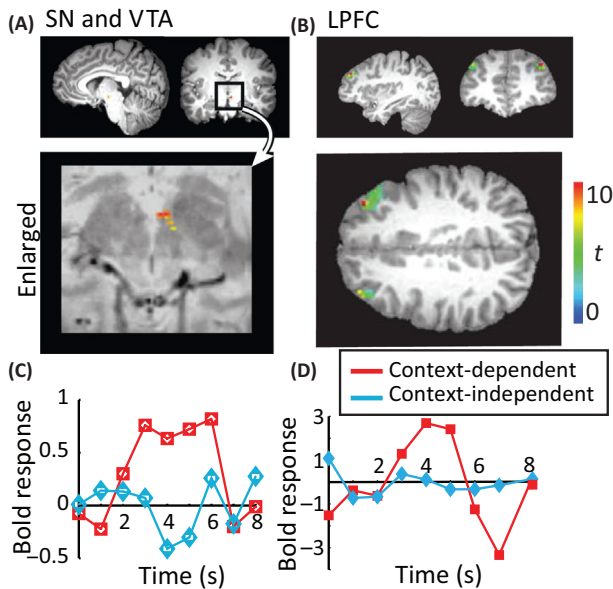
Dopamine Modulates Visual Signals in Cortex

Dopamine directly modulates visual signals represented by PFC neurons. In monkeys trained to detect faint visual stimuli, local application of dopamine in PFC altered the phasic stimulus-evoked responses of single neurons [76]. In one group of neurons, characterized by low-latency and phasic visual responses, dopamine reduced the background activity of the neurons while retaining visual responses. This effect increased the signal-to-noise ratio of the neurons (Figure 5). Such a response modulation may improve the ability of cortical networks to detect sensory events [77], causing an adaptive rescaling of its input so as to maximize information transmission [78,79]. In agreement with this idea, visual response latencies of PFC neurons are around 150 ms, and closely follow the typically observed 100–150 ms latencies of phasic dopamine signals [71,80,81]. Moreover, experimental application of dopamine quickly induced changes in the signal-to-noise ratio (within one trial, the temporal resolution of dopamine application). In addition, experimental D1R stimulation but not D2R stimulation improved encoding of visual items shortly after their presentation [82]. In a recent study, photostimulation of VTA neurons projecting to frontal cortex increased the signal-to-noise ratio of phasic frontal cortex neurons responses to aversive stimuli in mice [83]. Together, these findings suggest that dopamine directly modulates sensory input to PFC and gates behaviorally relevant information to be stored in prefrontal networks.

Dopamine is also known to affect the sensitivity, or gain, of sensory PFC neurons. Gain modulation in cortical networks can increase single-neuron signal detection performance [76,77]. In a distinct group of PFC neurons that were characterized by visual responses of long latency and duration, dopamine increased overall activity by **gain computation** [76,84]. Moreover, dopamine reduced the variability of neuronal responses [76]. Both effects are reminiscent of attentional modulation [85,86]. The same group of neurons showed a greater distinction between the absence and presence of a visual stimulus during detection, possibly preparing goal-directed evaluation of sensory signals. These findings suggest that, even at the stage of visual processing, dopamine operates in two modes: on the one hand, it gates short-latency visual signals in PFC by increasing their signal-to-noise ratio; on the other, it boosts long-latency visual signals by increasing gain and reducing their variability.

Dopamine not only influences the representation of visual signals within PFC but also in upstream visual areas that receive top-down signal from PFC. For example, on blocking D1Rs in the frontal eye field of monkey PFC, visual signals in V4 show higher amplitude, reduced variability, and increased between-neuron correlation [87,88] – all characteristics of a

in layer V neurons [26] which receive cortical input from superficial layers and project to downstream target areas [163]. D2Rs potentially increase the activity of deep-layer cortical neurons that relay motor signals. It is unclear if dopamine innervates these circuits directly or if volume transmission in the neuropil activates dopamine receptors. Abbreviations: L, layer; PV, parvalbumin; SOM, somatostatin.



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Figure 4. Dopamine Gates Sensory fMRI Signals in Human Prefrontal Cortex (PFC). (A) Functional imaging of dopaminergic midbrain substantia nigra (SN) and ventral tegmental area (VTA) following visual stimuli indicating contextual changes. Red areas correspond to areas strongly activated by contextual stimuli. (B) Functional imaging of lateral PFC (LPFC) (conventions as in A). (C) Time-dependent blood oxygen level-dependent (BOLD) responses show phasic midbrain dopamine activation following context-dependent cues. Note that the observed BOLD timecourse is predicted for a phasic activation following the hemodynamic response function. (D) Phasic activation of PFC followed SN/VTA activation (cf C; conventions as in C). Adapted, with permission, from [75].

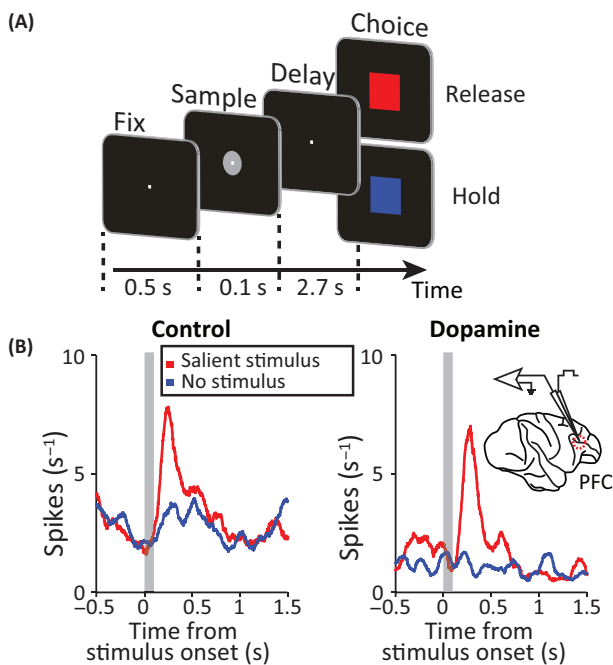


Figure 5. Dopamine Gates Sensory Signals in Monkey Prefrontal Cortex (PFC) Neurons. (A) Visual detection task, in which monkeys were required to detect faint visual objects (sample), followed by a delay period, before making a choice about the presence or absence of a visual stimulus (color cues). (B) A group of neurons showed fast, phasic activation following presentation of visual items (left). Dopamine inhibited the overall activity of the neurons while retaining phasic activation, consequently enhancing the neuronal signal-to-noise ratio (right). Dopamine impact on single neurons was investigated in lateral PFC using microiontophoresis (inset). Panels (E,F) adapted, with permission, from [76].

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top-down attentional signal provided by frontal cortex [85,86]. This attentional selection of visual information in upstream visual areas in turn boosts visual input to PFC 'tagged' by dopamine. Prefrontal dopamine therefore modulates both local processing of visual signals as well as visual signals in upstream areas.

Dopamine Physiology Allows Fast Modulation of Cortical Circuits

Dopamine modulates the sensory responses of PFC neurons via the two types of dopamine receptor families. How could the dopamine receptor families impact on neuronal processing at the level of neuronal microcircuits (Figure 3B)? Dopamine afferents in PFC form **synaptic triads** with putative excitatory (glutamatergic) synapses in layer II of the neocortex [89] that likely provide input from other cortical areas, including higher sensory areas [1]. D1Rs are found on postsynaptic structures such as dendritic spines and shafts [90] that could enable fast modulation of excitatory cortical input via D1Rs. D1Rs are known to decrease glutamate-induced excitatory postsynaptic currents *in vitro* [91–93], possibly decreasing the output firing of these neurons by a constant amount (**subtraction computation**), which in turn increases the relative strength of signals arriving in PFC compared to background noise (signal-to-noise ratio). In visual cortex, subtractive shifts of neuronal responses are mediated by somatostatin-expressing, dendrite-targeting interneurons [94], which might provide a second mechanism by which dopamine controls the flow of sensory input [95].

After the initial and rapid modulation by D1Rs, subsequent gain modulation of sensory signals might be mediated by D2Rs, which show excitatory effects *in vivo* [96,97]. In visual cortex, gain modulation is mediated by parvalbumin (PV)-expressing, soma-targeting interneurons [94]. D2Rs are particularly strongly expressed in PV-positive interneurons [32], and could mediate gain modulation by increasing interneuron excitability and thereby disinhibiting pyramidal cell firing [98]. Consistently, local activation of D2Rs *in vivo* increases the activity of many neurons in PFC [82,96,97,99].

Conclusion

Together, several lines of evidence point towards a mechanism by which dopamine provides a fast, phasic gating signal allowing sensory and contextual information to enter PFC circuits (Figure 3B). This gating mechanism likely first involves D1Rs that increase the neuronal signal-to-noise ratio by inhibitory mechanisms. A secondary gain computation that enhances sensory coding by excitatory mechanisms could be mediated by D2Rs. The main argument against a gating hypothesis is the reported slow and long-lasting dopamine levels in PFC [55]. However, provided that the onset of phasic dopamine signals is temporally precise, as evidenced from dopamine neuron activity [71,80], temporal precision for gating could be mediated by excitatory input [55].

Dopamine Influences the Maintenance and Manipulation of Information in Working Memory

Dopamine Modulation of Information Maintenance in Working Memory

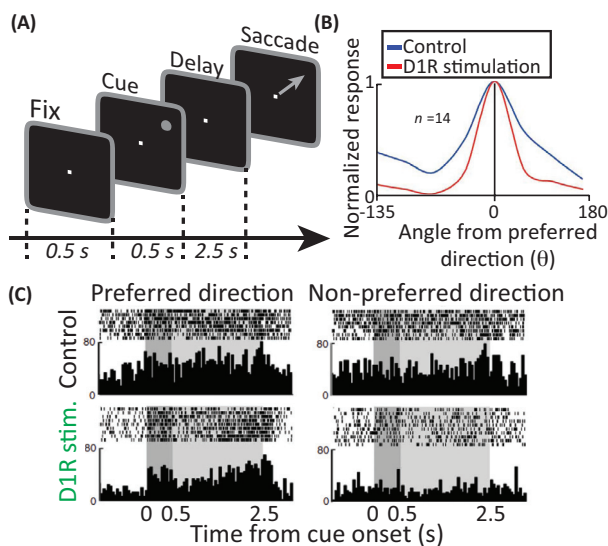
After relevant sensory signals have passed the initial input gate, they need to be maintained 'online' in brain networks (Figure 3A). As a fundamental ability for any complex behavior, the concept of working memory encompasses the capacity to retain immediately past information, to process this information contextually, and to use it to guide goal-directed behavior. A wealth of behavioral studies have established that prefrontal dopamine alters working-memory performance in humans and animals (e.g., [14,16,24] for review).

How do neurons maintain and manipulate information in working memory during a delay period? It is thought that neurons use sustained activity to actively buffer and process

information so as to bridge the temporal gap until an adaptive output response is selected [100–103]. Such persistent activity in the absence of external input is enabled by the recurrent connections within the active population of PFC neurons, such that excitation repeatedly re-enters neuronal circuits via recurrent loops, thereby keeping excitation alive (Figure 3C).

In primates, the impact of dopamine on spatial working memory has primarily been studied using the **oculomotor delayed response (ODR) task** (Figure 6A). In the ODR task, monkeys are required to make a saccade to a remembered spatial location after a memory delay period. At the behavioral level, systemically blocking D1Rs impairs spatial working memory in the ODR task [104,105], whereas stimulating D1Rs improves working memory performance in dopamine-depleted animals, but not in controls [106]. The effects of D1R activation is dose dependent and follows an inverted-U response curve, such that sub- or supraoptimal D1R activation is detrimental for working memory performance [14,107].

In agreement with these behavioral findings, dopamine influences the sustained activity of spatially tuned neurons during working memory, and the dose-dependency found in behavior is mirrored in the responses of PFC neurons. When locally stimulating D1Rs of PFC neurons during an ODR task (using a method called **microiontophoresis**), the spatial tuning of the neurons is enhanced at an optimal dose (Figure 6B,C), following an inverted-U response curve, with little stimulation having no effect and large stimulation having detrimental effects on tuning [108]. Blocking prefrontal D1Rs impairs spatial tuning [109], but has been also reported to improve spatial tuning of PFC neurons [110], presumably depending on the baseline tuning strength.



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Figure 6. Dopamine Modulation of Spatial Working Memory. (A) Oculomotor delayed response (ODR) task, in which monkeys must make a saccade towards a remembered spatial location of a cue followed by a delay period. (B) D1R stimulation sharpens the spatial tuning curve of prefrontal cortex (PFC) neurons, in other words increases the difference between the preferred and non-preferred stimulus directions of the neurons. (C) Single-neuron example of peristimulus time histograms (PSTHs) aligned to stimulus onset for the preferred stimulus direction (left) and non-preferred stimulus direction (right) of the neuron. D1R stimulation (stim.) inhibited the neuron, particularly for non-preferred target locations (bottom). Adapted, with permission, from [108].

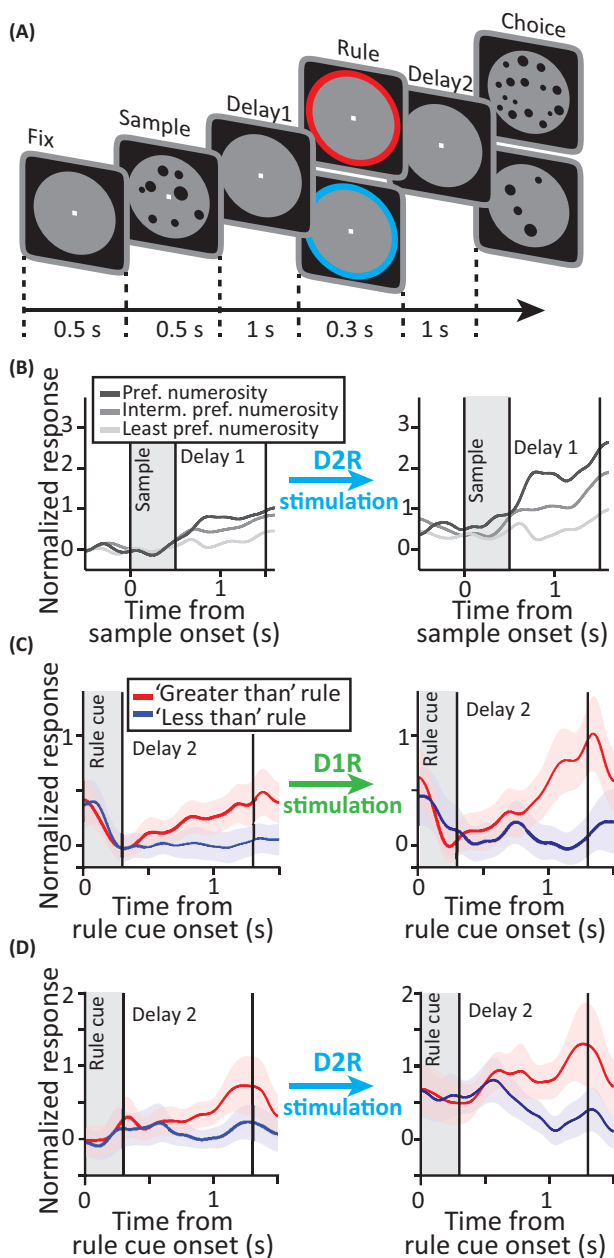
In monkeys required to perform a feature-based working-memory task by remembering the numerosity of a sample stimulus [111,112], namely the number of items in a visual display, the direction of D1R modulation during working memory depends on the cell type: in putative excitatory pyramidal cells, blocking D1Rs improved the encoding of numerosities, whereas stimulating D1Rs impaired it [113]. In putative inhibitory interneurons, however, the opposite pattern was observed. In this study, the stability of working-memory representations was tested by brief presentations of distracting, irrelevant stimuli during the delay period. This finding demonstrates that D1Rs potentially safeguard task-relevant prefrontal representations during working memory. Seemingly contradictory results of D1R effects in earlier studies [108–110] could be due to the differential impact of D1Rs on different cell types in addition to differences in dopamine baseline levels. This highlights the need to consider cortical cell types, which are known to play distinct roles in working memory and executive control [114–116], when assessing dopamine function in PFC.

The role of D2Rs in working memory has been less clear. At the behavioral level, D2R stimulation influences working-memory performance in humans and monkeys by increasing or decreasing performance [117–120]; these effects are dependent on the baseline performance of the subject [16] and do not follow a simple inverted-U relationship [121]. Blocking D2Rs often produced no effects on working-memory performance in the ODR task [105], but has also been shown to impair working-memory performance in humans [16,122] and monkeys [119]. It is therefore puzzling that early electrophysiological studies failed to find any effects on spatial mnemonic activity during the delay period in ODR tasks after stimulating or blocking D2Rs in PFC [97,110].

More recently, however, a prominent enhancement of sustained activity in the working-memory period induced by D2R stimulation was reported for PFC neurons in monkeys that performed a feature-based working-memory task requiring them to remember and match numerical quantity [99] (Figure 7A,B). These disparate findings in ODR tasks versus delayed number-matching tasks might relate to anatomically distinct PFC neuron populations that have been described for spatial and feature-based working memory [123], even though many single neurons represent both spatial and visual information [124]. In addition, the delay in the ODR task might reflect mainly motor preparation signals or allocation of spatial attention rather than maintenance of signals in working memory [4,125,126]. This is because the monkeys know from the onset of the sample location where they must make a saccade to in the subsequent test phase. Thus, the ODR task might entail specific cortical subcircuits capturing spatial processing signatures, which could be differentially modulated by dopamine receptors. Given that D2Rs did not modulate spatial working memory sustained activity [97], spatial information or motor preparation during the delay period might not be modulated by D2Rs.

Dopamine Modulation of Rules

Simply maintaining information ‘online’ is not sufficient. To guide goal-directed decisions, the content of working memory must be evaluated and manipulated according to behavioral principles, or rules. In humans, D1R availability in PFC is positively correlated with flexibly shifting between rules during a Wisconsin card-sorting test (WCST), a task probing the ability of a subject to flexibly shift between strategies [127,128]. Blocking D2Rs impairs shifting between response strategies in a variation of the WCST in which subjects were required to learn new visual discriminations based on different stimulus dimensions [129]. Stimulating D2Rs improves performance of subjects in a WCST [130], and increases functional imaging signals in frontal cortex during rule switching [131]. These findings lead to the conclusion that the contribution of dopamine to cognitive flexibility is mainly mediated by D2Rs [18], or by cooperative actions of D1Rs and D2Rs with complex dose–response functions [121].



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Figure 7. Dopamine Enables Maintenance of Objects and Rules in Working Memory. (A) In a rule-switching task, monkeys needed to remember the number of dots in visual display to successfully report if the sample numerosity was greater or less than the number of dots in a test display. During the memory delay period, the rule in effect was signaled by a visual cue (red ring, 'greater than'; blue ring, 'less than'). (B) D2R stimulation enhanced working memory of the visual item. The grey shaded area indicates sample presentation. Interm., intermediate; Pref., preferred. (C) D1R stimulation enhanced neuronal rule coding by slightly inhibiting background activity and boosting sustained activity. The grey shaded area indicates rule cue presentation. (D) D2R stimulation enhanced rule representation by increasing overall activity and decreasing relative activity to non-preferred items or rules. Adapted, with permission, from [99] and [82].

Animal studies assessing behavioral flexibility confirm the contributions of both D1Rs and D2Rs to behavioral flexibility. After rats learn to enter a specific arm in a maze based on either a spatial rule (e.g., ‘turn right’) or on a visual rule (e.g., ‘select arm with visual cue’), blocking prefrontal D1Rs impairs flexibly switching between the different response strategies or rules [19,132]. An even stronger influence was reported by blocking prefrontal D2Rs, which leads to an impaired performance by increasing perseverative errors, in other words rats maintain the same response strategy and need more trials to shift their strategy [19,133]. In monkeys that learned associations between arbitrary visual items and saccade directions separated by a delay period, blocking D1Rs in PFC impairs the ability of the animal to learn new associations, whereas the selection of familiar associations is not strongly affected [134]. Blocking D2Rs also impairs learning new associations, whereas stimulating D2R promotes perseverative errors [135]. Further, blocking either D1Rs or D2Rs reduces neural signatures of associations encoding the upcoming response in PFC [134,135].

As a neuronal correlate of rule switching, PFC neurons are known to flexibly group information according to overarching behavioral principles [136]. Such rule-selective neurons respond with an increase in discharge rate whenever their preferred rule has been cued during a delay phase [137–139]. The differential involvement of dopamine receptor families in rule switching was recently demonstrated in a study in which dopamine receptor-targeting drugs were micro-iontophoretically applied while recording single neurons in the PFC of behaving monkeys [82,140]. The task of the monkey was to switch between the two quantitative rules, ‘greater than’ and ‘less than’, while comparing the numerosity (number of dots) of two different visual displays separated by a delay period (Figure 7A). For any given trial, the rule in effect was signaled by a brief cue within the delay period, which allowed quantification on sustained neuronal rule coding responses during the delay. Rule-selective neurons differentiated between the two rules and responded to their preferred rule by firing rate increases. Both stimulation of D1Rs and D2Rs increased neuronal rule coding, albeit by different mechanisms: D1R stimulation decreased overall activity and enhanced activity to the preferred rule, thereby boosting the signal-to-noise ratio and improving rule encoding (Figure 7C). D2R stimulation, on the other hand, increased overall activity while relatively suppressing non-rule-related responses, thereby also increasing the signal-to-noise ratio (Figure 7D). This modulation was observed during a 1 s delay period, showing that both dopamine receptor families distinctly contribute to sustained neuronal rule coding of prefrontal neurons.

In monkeys employing a spatial rule, that is switching between pro- and anti-saccades based on a rule cue presented about 1 s before a go cue, D1R stimulation impaired sustained rule coding during the delay period [141]. However, D2R stimulation did not have any effect on rule coding. It is striking how these results parallel the contrasting findings for saccade-based spatial working memory and feature-based working memory [97,99,110]. Many factors might explain the disparate findings between studies using spatial and feature-based tasks, such as differences in baseline dopamine levels, diverse recording locations, and varying drug amounts. However, given the consistent findings for spatial and feature-based tasks, it seems more likely that dopamine has a distinct impact on prefrontal circuits involved in the two tasks.

Computational Models and the Roles of D1Rs and D2Rs

How can the effects of the two dopamine receptor families in working memory be accounted for mechanistically? Using biologically plausible computational models of **neuronal attractor networks** (Box 1 and Figure 8A,B; cf Figure 3C), a model was proposed in which D1R controls the stability of PFC representations [142,143]. In this model, D1R activation increases neuronal sustained responses to preferred stimuli as a neuronal correlate of working memory. At the

Box 1. Computational Models of Dopamine Action in PFC

Prefrontal working-memory processes can be implemented by biologically plausible computational models of neuronal networks [143,145,181]. The network architecture (cf Figure 3C, 8 A,B) relies on excitatory recurrent connections mediated by α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors. NMDA receptors have long postsynaptic currents, which allow integration of activity over longer timescales. Inhibitory connections from γ -aminobutyric acid (GABA)-ergic interneurons to pyramidal cells balance the excitatory drive, shaping selective responses of pyramidal cells by inhibition, in agreement with electrophysiological studies [114,182]. These attractor networks show two stable states: a spontaneous, low-activity state dominated by inhibitory currents, and a persistent, high-activity state of subsets of pyramidal cells with strong recurrent excitatory connections dominated by NMDA currents [145,183] – a prediction confirmed *in vivo* [148,184]. The persistent activity state is stable even without external stimulation. Importantly, these networks allow investigation of the potential mechanisms of dopamine action by changing synaptic conductances [142,145].

Dopamine mechanisms of action can be investigated by systematically changing different synaptic conductances in the model (based on *in vitro* studies) and evaluating changes in spontaneous or sustained activity (based on *in vivo* studies). Using this approach, dopamine has been proposed to balance the stability and flexibility of prefrontal networks [24,149]. In this framework, PFC networks are either in a D1R-dominated state, in which an increase in recurrent excitation by increasing excitatory NMDA currents and a decrease in spontaneous activity by increasing inhibitory GABA currents stabilizes representations in working memory [142,144] (Figure 8C). Conversely, a D2R-dominated state with opposite mechanisms reduces inhibition in the network, allowing spontaneous transition between high- and low-activity states, thereby producing unstable representations and thus enabling switching between different representations. These states might be controlled by time: dopamine could first support dynamic updating of prefrontal representations via a D2R-dominated state, and subsequently stabilize a limited amount of representations via a D1R-dominated state, shutting down irrelevant representations and safeguarding representations from distractors [24,149]. Note that recent electrophysiological evidence rejects a D2R mechanism of action which is simply opposite of D1R [99], and instead supports a mechanisms by which D2Rs increase both spontaneous and sustained activity by increasing interneuron excitability (Figure 8D).

This dual-state theory of prefrontal dopamine function has been linked to clinical symptoms of schizophrenia, forming the attractor hypothesis of schizophrenia [185]. In this model, excessive D2R activation produces unstable representations in PFC that lead to positive symptoms such as hallucinations and intrusion of thought [186]. Accordingly, blocking D2Rs is the common mechanism of all antipsychotic drugs used to treat the positive symptoms of schizophrenia [187]. The attractor hypothesis of schizophrenia parallels a suggestion that the positive symptoms in schizophrenic patients are caused by dopamine assigning aberrant salience to sensory stimuli [188]. Mechanistically, dopamine could attribute aberrant salience to sensory or mnemonic events by gating these events to PFC or by altering the properties of PFC networks to allow switching between representations (see main text).

same time, spontaneous activity (in the absence of a memorized item) is decreased. Both effects increase neuronal selectivity during working memory. These effects were mediated by two mechanisms in the model. First, the spontaneous activity of pyramidal cell was decreased by an increase of inhibitory GABA currents. Second, sustained high-activity states were enhanced by increasing excitatory (glutamatergic NMDA) currents (Box 1 and Figure 8C) [144,145]. D1R-induced inhibition might be mediated by amplifying inhibitory postsynaptic currents in pyramidal cells [146], or by weakening non-NMDA glutamatergic responses [92]. At the same time, D1R stimulation shows a specific excitatory effect *in vitro* by potentiating only NMDA-evoked responses [92,147], which boosts NMDA-dependent sustained activity [148]. This model recapitulates major findings from *in vivo* studies [82,99,108–110,141].

Recently, the same model architecture has been used to implement D2R modulation of prefrontal networks [99]. By extrapolating results found during *in vitro* recordings in brain slices [98,146,149], it was suggested that D2R stimulation decreases inhibitory currents in pyramidal cells while at the same time increasing interneuron excitability, thereby maintaining an excitation/inhibition balance [99] (Figure 8D). This model recapitulates major results from *in vivo* studies, namely a D2R-induced increase in spontaneous activity as well as an enhancement of rule and working-memory coding [82,99]. The model therefore provides a possible circuit mechanism for how D2Rs modulate PFC networks underlying executive control.

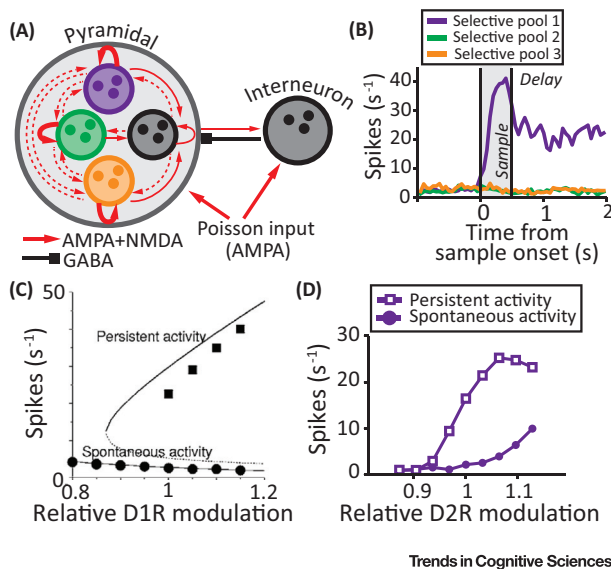


Figure 8. Computational Model of the Role of Dopamine in Maintaining Information in Prefrontal Cortex (PFC). (A) Attractor network model implementing the same basic circuitry as in Figure 3C using a network of leaky integrate-and-fire neurons. In this model, pyramidal cells form stimulus-selective pools by forming stronger recurrent excitatory connections within a pool (thick arrows) versus connections outside a pool (thin and dashed arrows). A pool of inhibitory neurons balances excitation and inhibition. (B) After stimulation (excitatory drive to a selective pool), the network maintains bistable states even without further input (purple pool). (C) Proposed D1R stimulation increases recurrent activity while at the same time decreases spontaneous activity during the delay period. (D) Proposed D2R stimulation increases persistent activity during the delay period. Adapted, with permission, from [99] and [145].

Complementary Dopamine Receptor Roles in Adapting Prefrontal Networks

Cognitive control relies on a fine balance between stability and flexibility: behaviors that are adaptive need to be maintained by stable brain states, whereas changes in the environment or internal states of an organism require switching between response options and their underlying brain states to avoid maladaptive behaviors. The modulatory dopamine system is known to be involved in dynamically regulating these computational tradeoffs [150], thereby motivating the cognitive cost of executive control [151]. This is realized in attractor network models that propose that dopamine balances between the two states – stability and flexibility – of prefrontal networks [24,149] (Box 1). In a D1R-dominated state, dopamine stabilizes prefrontal representations by increasing sustained responses during working memory [142,144]. By contrast, a D2R-dominated state renders prefrontal representations unstable, thus enabling switching between representations via a D2R mechanism opposite of D1R [152].

However, this dual-state model does not account for recent evidence suggesting a D2R mechanism that is not strictly opposite of D1R (as suggested in [152]), but instead entails distinct physiological mechanisms that also lead to enhanced sustained responses [99]. These findings do not necessarily reject the dual-state theory because elevated firing rates during sustained neuronal responses might be more susceptible to interference and thereby render prefrontal attractor states less stable. Indeed D2R stimulation increases the dynamic properties of neuronal populations in PFC and boosts the rate of change between different activity patterns [99]. D2R-induced increase of the responsiveness of PFC neurons was apparent at the beginning of delay periods, and promoted updating of task-relevant information, possibly by fast and transient recruitment of inhibitory interneurons [55]. It remains to be resolved if a biophysical model implementing proposed D2R mechanisms would capture both the dynamic

properties of prefrontal neurons and the enhancement of sustained responses during delay periods.

Dopamine Physiology Timescales Underlying Flexibility and Stability

Action potentials in dopamine neurons are assumed to be the principal trigger for dopamine release at the axon terminals (more precisely, via varicosities or synapses). The phasic discharges lead to a sudden and brief release of dopamine that is ideally suited to explain the gating mechanism discussed in the previous section. However, during the delay, for instance between a conditioned stimulus and reward delivery, dopamine neurons are not active [153,154]. If dopamine neurons are silent during delays, how can the concentration of dopamine in PFC change to influence working-memory processes seconds after perceiving a stimulus? Part of the answer is that dopamine levels in PFC are often long-lasting, in the order of seconds and minutes [50,55,56]. Even more important is the finding that release of dopamine is not only caused by the discharges of dopamine neurons but can also be influenced by local interactions at the presynaptic terminal endings of dopamine neurons. Neurotransmitters acting on terminals can cause local release of dopamine, irrespective of the activity of such dopamine neurons [155]. For example, activation of cholinergic interneurons triggers dopamine release via the activation of nicotinic receptors on dopamine axons [156]. It is tempting to speculate that this local mechanism acts at a much slower timescale [43,155], and potentially at timepoints during a trial in which dopamine neurons are not phasically activated, such as during delay periods of a task.

Moreover, differential receptor affinities and distributions could allow fast as well as long-lasting dopamine effects in PFC [55,56]. Dopamine is broadly distributed because varicosities from dopamine neuron fibers are found in all cortical layers [157]. In addition, many D1R and D2R receptors are located remotely from synapses (extrasynaptically) on PFC neurons [31,158] and become activated by dopamine diffusion in the **neuropil** [159]. It is therefore conceivable that a temporally precise and D1R-mediated gating signal first entrains synaptic triads (see above). This effect could be followed by a D2R-dominated state that activates high-affinity, extrasynaptic D2Rs [24,160]; the latter process would allow prefrontal dynamical networks to update working-memory content based on task demand. Finally, a D1R-dominated state activating low-affinity extrasynaptic D1Rs could stabilize sustained prefrontal representations, thereby safeguarding PFC activity from interference [24,113,161].

Conclusion

The evidence reviewed here points to a complementary role of D1R and D2R in cognitive control (Figure 3C). Both receptors modulate sustained working memory and rule-related responses, albeit by distinct mechanisms. These mechanisms entail modulation of synaptic currents, giving rise to sustained neuronal responses as well as interneuron-to-pyramidal signaling. Dopamine thus differentially modulates the different cell types and circuits required for executive control. This mechanism is likely linked to the role of dopamine role in gating: gain computations of sensory signals during gating could be a part of a D2R-driven dynamic updating system, corroborated by the similar timecourses observed for gain computations and D2R-mediated dynamic population responses in PFC [76,99].

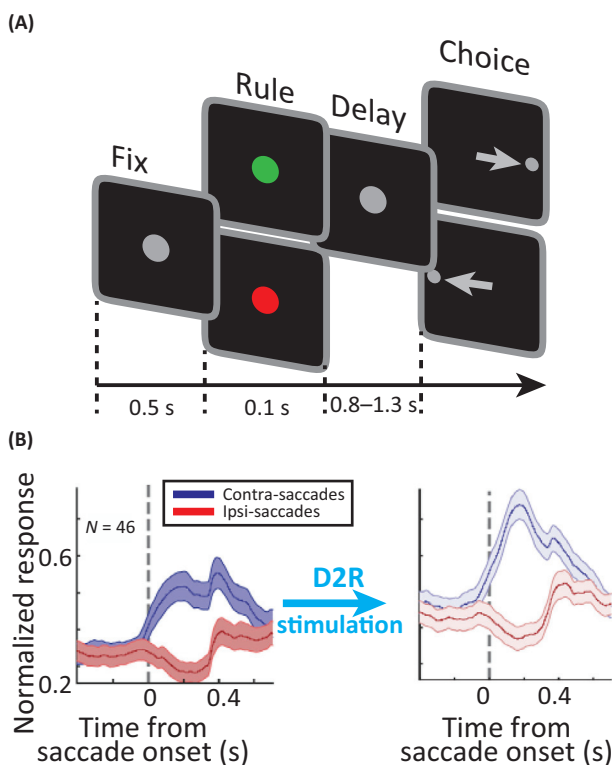
Dopamine Controls Cortical Premotor Signals

D2Rs Modulate Motor Signals

Once the incoming sensory information has been evaluated according to the rule of the game, an appropriate motor plan must be generated and executed. In the telephone example used in the introduction, this amounts to actually picking up the telephone if it is ringing at our home. Dopamine has been found to also influence this third function in the temporal sequence of a cognitive delay task – the relaying of motor commands to motor structures.

In PFC, microinfusion of D1R antagonists or D2R agonist in the frontal eye field (FEF) biases the selection of a target towards the response field of the infused FEF patch [87]. Interestingly, visual responses in higher visual areas (V4) were affected by D1R but not D2R manipulation. This finding corroborated a model in which D2Rs are abundant in layer V neurons [26] and project to superior colliculus to drive biased saccadic target selection (Figure 3D) [88,162]. Because the majority of layer V neurons are subcortical-projecting neurons, including corticotectal neurons which do not project to cortical targets [163–165], D2R manipulation would not directly modulate cortical signals. D1Rs, on the other hand, are prominently present in all cortical layers [26] and could directly modulate corticocortical projections to V4.

These reports parallel findings that D2Rs modulate motor preparation signals in PFC. During spatial working memory probed by the ODR task, D2R manipulation selectively altered neuronal responses before and after saccade onset, while leaving sustained activity during spatial working memory unaffected [97]. In monkeys trained to switch based on preceding rule cues between pro- and anti-saccades towards or away from a target at random spatial locations (Figure 9A), D2R stimulation did not influence spatial rule signals during the delay period, but it did enhance pre- and post-saccadic activity [141]. In addition, D2R stimulation



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Figure 9. Dopamine Controls Relaying of Motor Signals. (A) In a spatial rule-switching task, monkeys were required to perform either a pro-saccade towards a go cue or an anti-saccade away from a go cue. The rule in effect (pro- or anti-saccade) was signaled at the beginning of a trial by a green or red circle, followed by a delay period and target presentation. (B) Recording in lateral prefrontal cortex (PFC) combined with microiontophoretic drug application revealed that D2R stimulation enhances peri-saccadic activity even before the monkeys made a saccade. This effect was mainly observed for saccades towards the contralateral hemifield (contra-saccades). Adapted, with permission, from [141].

increased the reaction times of the monkey for saccades and lever releases [82,141]. This effect was stronger when monkeys made pro-saccades towards their contralateral field of view (Figure 9B). These results suggest that D2R-modulated neurons participate in saccadic target selection and motor initiation in primates by relaying premotor signals to downstream target areas.

Conclusion

D2Rs modulate motor signals, suggesting a specific role in relaying motor commands to downstream areas preparing behavioral responses. Interestingly, dopamine gates actions and action sequences through projection to the striatum [166,167], an area strongly innervated by layer V prefrontal neurons. Possible interactions between mesocortical and mesostriatal dopamine systems are unknown.

Concluding Remarks

We have outlined how prefrontal dopamine enables successful cognitive control in three domains. First, dopamine gates sensory input via fast modulation of excitatory glutamatergic afferents. Second, dopamine allows updating of prefrontal representations as well as subsequent stabilization through complementary dopamine receptor mechanisms. Finally, dopamine controls the flow of information to downstream target areas preparing motor commands. This account has various implications for future studies addressing the impact of dopamine on prefrontal circuits (see Outstanding Questions).

First, it underscores the importance for task diversification when studying the functional role of dopamine. Because different tasks require distinct aspects of executive control, they likely recruit different prefrontal microcircuits that are distinctly modulated by dopamine. Different tasks would disentangle the role of dopamine in these three domains which are separable by their timescales and task demand. For example, it remains to be determined how D2Rs enable flexible switching between working-memory content at the level of single neurons or populations. Using working-memory tasks with distracters or tasks that require switching between rules or contexts at precise moments while measuring neuronal activity and manipulating dopamine receptors could directly test how D1Rs and D2Rs mediate stability and flexibility during executive control. Furthermore, many tasks use a single or only a few motor behaviors, such as eye movements, to record the choice of an animal. It remains thus unclear if and how dopamine is involved in relaying different types of motor commands in prefrontal cortex. Using tasks with diverse motor behaviors could test if prefrontal dopamine has a generalized role in relaying motor commands that is not unique to specific motor commands such as eye movements.

Second, understanding the role of dopamine in PFC requires knowledge about cell types, circuit recruitment, and neuronal computations. For example, emerging evidence shows that dopamine differentially impacts on cortical cell types involved in different aspects of executive control. The contribution of different cell types to cognitive control, as well as the impact of dopamine on different cell types, can be studied with emerging optical tools in primates [38,168]. In addition, making use of rodent or corvid models of executive control and cross-species comparisons of executive functions [169,170] could accelerate our understanding of prefrontal dopamine.

Finally, it is necessary to study the midbrain dopamine signal during executive control. Although much is known about how reward expectation and saliency drive dopaminergic neurons, precise recruitment of dopamine neurons and dopamine release in PFC during executive

Outstanding Questions

Given our account of the threefold role of dopamine in executive control – when and how are dopamine neurons recruited during different aspects of executive control?

How do dopamine and dopamine receptors modulate the activity of different cortical cell types during behavior?

How do dopamine and dopamine receptors impact on cortical subcircuits subserving different aspects of cognitive control? What is the influence of dopamine receptors in different behavioral tasks segregating cognitive functions?

Can we reconcile reinforcement learning theory with theories of prefrontal functions? Alternatively, does dopamine assume distinct roles in learning and motivation, as well as in cognitive control?

control is largely unclear. Moreover, dopamine neurons are not uniform and show different response profiles according to their anatomical location and projection target [171–175]. Studying the response profiles of different dopamine neurons could help to reconcile the seemingly distinct roles of dopamine in learning, motivation, and cognitive control depending on the target area [151,176,177,178]. For example, prefrontal neurons engaged in cognitive control are modulated by reward size [179,180]. Understanding the likely role of dopamine in the interaction between reward signals and cognitive control signals could help to bridge the gap between learning and motivating cognition and action. Disentangling the diverse computational roles of dopamine in goal-directed behavior might help in understanding the vulnerability of the dopamine system underlying complex psychiatric diseases.

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