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Dopaminergic control of the striatum for high-level cognition

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Dopamine has long been implicated in a wide variety of high-level cognitive processes, ranging from working memory to rule learning and attention switching. Notable progress has been made in the past decades, but the mechanisms underlying effects of dopamine on high-level cognition remain unclear. This article reviews evidence for an important role of the striatum and its interaction with the prefrontal cortex and suggests a variety of ways by which changes in dopamine transmission can bias high-level cognition.

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Introduction

Dopamine has long been implicated in behavioral control. Particularly well known are its contributions to reward learning [1,2••,3,4]. More specifically, dopamine has been associated with a class of learning that, in the instrumental domain, echoes Thorndike's habit learning of automatized responses through reinforcement. This form of dopamine-dependent habit learning is thought to be regulated by a model-free system that has been associated with the dorsolateral parts of the striatum. It is defined based on its insensitivity to changes in outcome value and instrumental contingency and is often contrasted with a form of goal-directed behavior that is regulated by a model-based system [5,6]. Unlike habitual behavior, which is hardwired by reinforcement and directly based on experience, goal-directed behavior involves flexible, forward planning using internal representations (models) of the environment [7] and is directly sensitive to changes in outcome value and contingency [8]. While signals associated with model-based, goal-directed control have been found throughout the brain, including the prefrontal cortex, hippocampus, and dorsomedial striatum [9,10••,11,12••,13,14], current formal theories of reinforcement learning offer no obvious role for dopamine in model-based control [5,15,16].

This conceptualization of dopamine as serving exclusively model-free behavior is apparently at odds with empirical evidence demonstrating effects of dopamine on high-level cognitive control processes, such as working memory, complex rule learning and attention switching [17,18••,19–21]. Indeed high-level cognitive deficits are core to many dopamine-related disorders, such as addiction [22] and Parkinson's disease (PD) [23]. Performance on tasks that typically involve model-based forward planning, such as the one-touch Tower of London and self-ordered spatial search tests, is sensitive to dopamine manipulation in PD patients [24], healthy volunteers [25], and nonhuman primates [26].

Furthermore, certain effects of dopaminergic drugs on tasks of learning are difficult to account for by modulation of a model-free, habitual system, and rather seem to involve behavior that depends on explicit models of the environment [19,20,27]. For example, Cools *et al.* [28••] have shown effects of dopamine receptor stimulation and dopamine synthesis capacity on a deterministic form of one-trial reward and punishment prediction learning. Although it is tempting to interpret these effects in relation to the standard framework of model-free reinforcement learning, performance on the task probably does not involve any model-free control, but rather depends on the ability to update explicit 'cognitive' predictions of future reward or punishment.

In addition, the body of neurophysiological work that originally inspired the hypothesis that dopamine is involved in model-free, habit learning has recently been extended with new data showing that even the midbrain dopamine neurons themselves encode signals that could support model-based, goal-direct control [29,30]. For example, Bromberg-Martin and Hikosaka [29] have shown that midbrain dopamine neurons that encode reward expectation also encode information expectation, suggesting that dopamine plays a role not just in reward seeking but also in information seeking.

These different lines of evidence suggest that effects of dopamine go beyond the modulation of model-free, habitual behavior [31], and extend to high-level cognitive processes. In this review, a variety of mechanisms will be addressed by which high-level effects of dopamine may arise. Two factors should be kept in mind. First, midbrain dopamine neurons are known to project to brain regions associated with model-based control, for example, the

prefrontal cortex, the dorsomedial striatum and the hippocampus. Second, although there might be separate model-free and model-based systems for behavioral control [5], these systems are unlikely to act in isolation. In particular, the prefrontal cortex is well known to interact with the striatum in part-segregated, part-interactive fronto-striatal circuits [32–34]. Accordingly, dopamine might affect high-level cognitive function by altering flow through these circuits. Various instantiations of such fronto-striatal circuit effects are discussed.

Direct dopaminergic control of high-level cognitive function

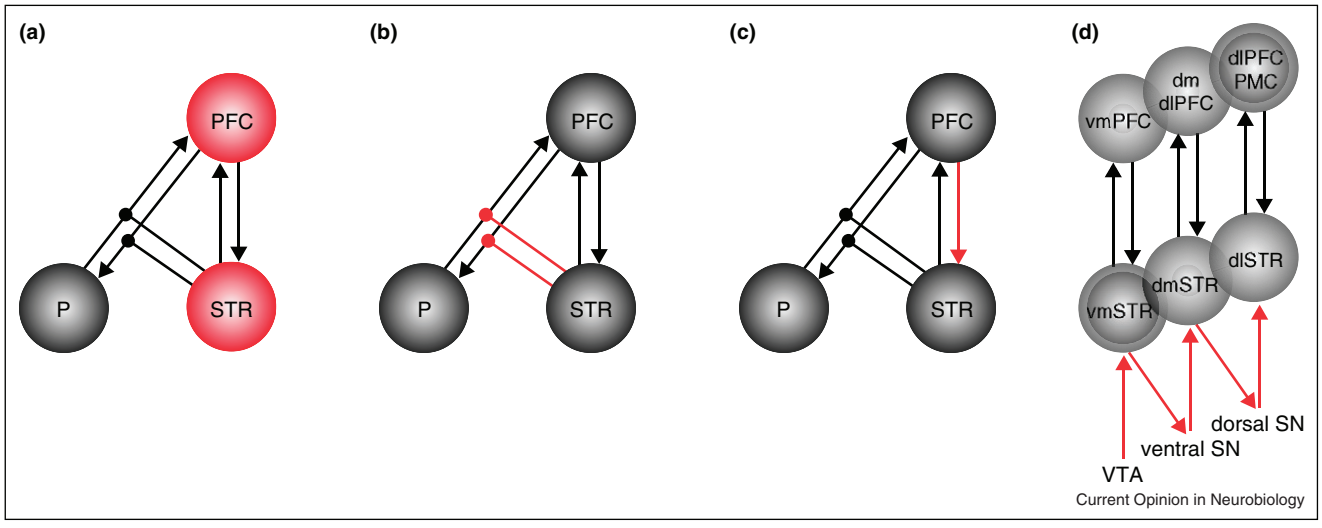
Dopamine neurons project not only to the dorsolateral striatum, associated with model-free behavior, but also to regions implicated in model-based, goal-directed behavior. Accordingly, dopamine probably modulates high-level cognition by acting directly in these brain regions (Figure 1a). For example, dopamine receptor stimulation in the prefrontal cortex contributes to goal-directed behavior by modulating the persistent, short-term memory of goal-relevant representations, perhaps via suppression of goal-irrelevant signals [35–37]. This could happen by stimulation of D1 receptors, which is thought to optimize 'quelling' or 'sculpting' of activity in the most strongly active cell assemblies. Such 'quelling' would occur by increasing the impact of the NMDA (*N*-methyl-D-aspartate) component of excitatory synaptic input onto prefrontal neurons, thought to be essential for the maintenance of current prefrontal cortex activity. It could also reflect increases in the excitability of inhibitory GABA-ergic inter-neurons, which hypothetically attenuate the strength of further excitatory input [38]. Additionally, this could happen by stimulation of D2 receptors primarily localized on layer V cells in the prefrontal cortex that send descending projections, for example, to the posterior cortex, thus enabling the biasing of competition between goal-relevant and goal-irrelevant representations.

Evidence indicating that the catecholamine-*O*-transferase gene, which primarily controls dopamine in the prefrontal cortex affects exploratory decisions during a learning task suggests another way by which direct modulation of the prefrontal cortex can affect behavior that goes beyond habit learning [39].

Furthermore, dopamine contributes to goal-directed behavior by acting directly on dopamine receptors in the hippocampus, thus modulating persistent, long-term memory of places and new paired associates [40,41]. In addition, the incorporation of hippocampus-dependent information in goal-direct planning of future actions has been shown to depend on direct dopamine receptor stimulation in the prefrontal cortex [42].

Finally, the guidance of behavior by current goals might depend on direct action at dopamine receptors in the dorsomedial striatum, as suggested, for instance, by findings that infusion of the neurotoxin 6-hydroxydopamine

Figure 1



Simplified schematic of multiple mechanisms by which dopamine could alter high-level cognition. Actions of dopamine are represented in red. **(a)** Dopamine acts directly within brain regions associated with high-level cognitive functions, for example, the prefrontal cortex (PFC) and the dorsomedial striatum. **(b)** Dopamine in the striatum (STR) regulates an 'input gate' to control cognitive and motor representations in the prefrontal cortex, as well as an 'output gate' to control cognitive and motor representations outside the prefrontal cortex, for example, in posterior regions (P). **(c)** Dopamine in the striatum modulates the impact of top-down influences from the prefrontal cortex on the striatum. **(d)** Dopamine modulates interactions between distinct fronto-striatal circuits.

selectively in the dorsomedial striatum (not extending to the dorsolateral striatum) attenuated sensitivity of lever-press responding to action-outcome contingency degradation [43].

Dopaminergic control of high-level cognition via the striatum

In addition to affecting high-level cognition by modulating model-based systems directly, dopamine affects cognition indirectly via modulating processing in the dorsolateral striatum, thus altering flow through dorsolateral fronto-striatal circuitry (Figure 1b). Empirical evidence for the hypothesis that dopamine in the striatum can affect prefrontal function comes from genetic and neurochemical imaging work, revealing that variation in striatal dopamine function is associated with altered neural efficiency not only of the (dorsolateral) striatum [44,45] but also of the prefrontal cortex and associated working memory updating and attention switching [46–49].

The general principle underlying the mechanism by which the striatum selects representations for working memory updating, abstract rule learning and high-level attention switching might be the same as that for habits [1,50]. According to this account, the likelihood that a cognitive representation is selected for abstract learning or updating of attention/working memory in the prefrontal cortex is proportional to the difference between activity for that representation in the Go and NoGo pathways of the striatum. Thus signals in the striatum might constrain the mechanisms that regulate input to the prefrontal cortex, either from posterior cortex regions [51] (Figure 1b), or from the striatum itself.

By analogy, the output of the prefrontal cortex, in either sensory or motor terms, might also be controlled by activity in the striatum (Figure 1b) [50]. Empirical evidence for this hypothesis came from a recent functional magnetic resonance imaging study in healthy volunteers, in which subjects switched between attending to the faces or the scenes of overlapping face/scene stimuli [52••]. The switches were accompanied by potentiation of goal-relevant representations relative to goal-irrelevant representations in stimulus-specific posterior visual cortex (fusiform face area and parahippocampal place area), presumably reflecting top-down biases from the prefrontal cortex. The striatum played a crucial role in regulating such attention switching by gating the top-down bias from the prefrontal cortex on stimulus-specific posterior cortex. Dopamine could alter such top-down biasing of competition between goal-relevant and goal-irrelevant representations via stimulation of dopamine receptors on striatal neurons, altering the balance between activity in the Go and NoGo pathways and lowering the threshold for gating top-down influences.

Dopaminergic control of top-down influences on striatal function

A third mechanism by which dopamine might affect high-level cognition is by altering top-down influences of the prefrontal cortex on striatal processing (Figure 1c). For example, instructed rules can exert powerful control over learning-based choice, so that subjects follow the instructed rule rather than experience [53] and such effects are accompanied by modulation of striatal activity [54,55]. Computational modelling work has indicated that this top-down bias might well reflect an effect of the prefrontal cortex on the striatal system, so that learning is biased by instruction rules, with the impact of rule-consistent outcomes being amplified and that of rule-inconsistent outcomes being suppressed [53]. This could be instantiated by top-down excitatory (glutamatergic) input to striatal neurons on which dopamine receptors are located, thus modifying dopamine-triggered synaptic plasticity. The hypothesis that top-down information modifies the input to a habitual, model-free system concurs with observations that dopaminergic drugs can alter prefrontal cortex input to the striatum [42], and also accounts for recent neural data showing that learned rules (values derived from model-based learning) can alter reward prediction error signals in the striatum [12••].

The suggestion that cognitive, model-based mechanisms in the prefrontal cortex bias the input to the habitual, model-free striatum raises the question whether the firing pattern of dopamine neurons in the midbrain can also be influenced by top-down model-based systems [29]. Although this remains to be tested, there is now extensive empirical evidence that interference with prefrontal cortex function via excitatory or inhibitory transcranial magnetic stimulation can indeed alter dopamine release in the striatum [56••], a finding that underlines the possible coordination rather than competition between the prefrontal cortex and the striatum. If model-based, cognitive mechanisms in the prefrontal cortex bias the input to the striatum, then it is not surprising that causal manipulations of striatal dopamine can alter the impact of top-down models or rules on behavior.

Dopaminergic control of interactions between distinct fronto-striatal circuits

A fourth mechanism by which dopamine in the striatum could affect high-level, model-based cognitive control is by altering hierarchical interactions between distinct cortical systems that converge in the striatum (Figure 1d). A role for striatal dopamine in mediating hierarchical interactions between distinct fronto-striatal circuits is plausible given the arrangement of spiraling connections between the midbrain and the striatum; this arrangement is perfectly suited to subserve a mechanism by which dopamine directs information flow from ventromedial fronto-striatal circuitry via dorsomedial fronto-striatal circuitry to dorsolateral fronto-striatal circuitry [57].

One functional instantiation of this arrangement is the transformation of incentive motivation and information about the values of goals, contexts and actions into both abstract cognitive and concrete action choices. Aarts *et al.* [58] provided evidence for a crucial role of striatal dopamine in mediating interactions between incentive motivation and high-level cognition by showing that effects of incentive motivation on attention switching were accompanied by changes in activity in the striatum, and that these changes varied as a function of genetically determined baseline levels of striatal dopamine. This relates to ideas about dopamine playing a key role in the mechanism by which reward prediction signals that are conveyed by the so-called 'critic' (associated with Pavlovian learning mechanisms and the ventromedial striatum) teach action choices that are conveyed by the so-called 'actor' (associated with instrumental learning mechanisms and the dorsal striatum) [8,59–61]. Given that both the Pavlovian 'critic' and the instrumental 'actor' might be further subdivided in model-based and model-free components [7], this arrangement allows for multiple ways in which dopamine could affect model-based, goal-direct behavior via altering model-free Pavlovian control [2••,62]. This is particularly pertinent given the clear role of striatal dopamine in the invigoration of instrumental responding [63], and in effort-based decision making [64–66], both of which have been linked formally with Pavlovian effects of dopamine via modulation of expected reward rate [67].

Ideas about a role for dopamine in hierarchical interaction between distinct fronto-striatal circuits are reminiscent of notions regarding hierarchically nested, cascading fronto-striatal circuits that subserve the discovery of abstract hierarchical rules [3,68,69] and the development of skills or temporally abstract 'macro-actions' [70]. In each of these cases, hierarchical structure is proposed to emerge through interactions between more anterior and/or ventral prefrontal cortical regions and more posterior and/or dorsal prefrontal cortical regions. The suggestion that these interactions are indirect and mediated by the striatum is supported by empirical observations that activity in nigrostriatal circuits is dynamically reorganized during the emergence of action sequences [71–73].

Conclusion

Effects of dopamine in the striatum go beyond the modulation of model-free, habitual behavior, and extend to high-level cognitive processes, including working memory, abstract rule learning and high-level attention switching. This review highlights multiple mechanisms underlying such cognitive effects. Dopamine may alter high-level cognition by acting directly on model-based structures, such as the prefrontal cortex or the hippocampus, or by indirect modulation of striatum-gated input or output of model-based structures. Furthermore, dopamine might act by modulating hierarchical interactions between distinct fronto-striatal circuits, thus modulating interactions between distinct model-based and model-free systems.

We are far from a complete account of dopamine's effects on high-level cognition. This partly reflects the large individual variability in dopamine's effects due to the existence of multiple inverted-U shaped relationships between dopamine and cognition [17]. However, an additional factor of uncertainty concerns the model-based, goal-directed status of many of dopamine's effects on high-level cognition. Indeed, according to one hypothesis, various high-level cognitive effects of dopamine in fact reflect modulation of model-free Pavlovian control [15]. The precise nature of dopamine's role in high-level cognition needs to be established in future work by adopting contemporary operational criteria of the distinct forms of model-based versus model-free, and Pavlovian versus instrumental control of behavior [6,8]. Such behavioral analyses should be combined with pharmacological approaches that leverage current knowledge about baseline-dependency of dopamine's effects.

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