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The cost of dopamine for dynamic cognitive control

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Cognitive control helps us attain our goals by resisting distraction and temptations. Some of us strive to enhance it beyond normal, for example by means of dopaminergic medication like methylphenidate. However, the cognitive effects of such smart drugs are unclear. What we need is an understanding of the mechanisms by which dopamine modulates cognitive control. Advances in cognitive neuroscience highlight a role for dopamine in cost–benefit decision-making. I build on these advances by re-conceptualizing cognitive control as involving not just prefrontal dopamine, but also modulation of cost–benefit decision-making by striatal dopamine. This approach will help us understand why we sometimes fail to (choose) to exert cognitive control, while also identifying mechanistic factors that predict dopaminergic drug effects on cognitive control.

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Introduction

Cognitive control is a poorly defined term, but can be broadly conceptualized as the set of mechanisms required for pursuing a goal, especially when distraction or competing responses must be overcome. One key aspect of cognitive control is the ability to maintain, stabilize and focus on current goal-representations. This ability is particularly well developed in human animals, but failures of cognitive control and focus are common, not only in neuropsychiatric disorders such as attention-deficit(/hyperactivity) disorder (AD(H)D) and addiction, but also in healthy states such as fatigue or stress. Cognitive control deficits can be remedied using medication that increases dopamine and noradrenaline, such as methylphenidate and modafinil [1,2]. Methylphenidate acts by blocking the dopamine and noradrenaline transporter and is used to combat cognitive control deficits, seen in disorders like AD(H)D, but also increasingly so by healthy people for cognitive enhancement, as smart pills. Estimates of the proportion of healthy students using drugs like methylphenidate off-label range from 4% to 16% [3]. One problem is that smart drugs do not help everyone in every context. Effects of catecholaminergic drugs, such as methylphenidate and modafinil, vary greatly, not only across individuals, but also across tasks. The same drug can improve cognitive performance in one context, while impairing it in another, depending on task demands. Resolving the large variability in catecholaminergic drug effects is a key scientific puzzle and requires an understanding of the neurocognitive mechanisms by which dopamine and noradrenaline alter cognitive control. In this review I focus on dopamine's role in cognitive control, while recognizing that another key challenge for research ahead is to disentangle dopamine's from noradrenaline's role in the mechanisms discussed below. Specifically, following prior work [10], I argue that dopaminergic drugs have different cognitive effects depending on the neural locus of their action, with prefrontal and striatal dopamine having opposite effects on our tendency to stabilize current goal-representations. Here I progress beyond these prior observations by beginning to assess the mechanisms underlying the contribution of striatal dopamine to cognitive control.

One first step towards such progress in our understanding of dopamine's role in cognitive control involves a redefinition of cognitive control that extends beyond the common emphasis on persistence, for example, on the ability to maintain, focus and stabilize current goal representations and protect them against distraction. Adaptive behaviour depends not just on cognitive focus and stabilization but, given the many changes in our environment, requires instead a dynamic equilibrium between the distinct, opponent cognitive actions of goal-stabilization, important for a cognitively focused state, and goal-destabilization, important for a cognitively flexible state.

The next step is to determine how we arbitrate between these different cognitive states involving goal-stabilization and goal-destabilization. This involves re-conceptualizing cognitive control as a cost–benefit decision instead of solely an implementation challenge. Classic prefrontal models of cognitive control address primarily our ability to implement control. Recent advances have led to a shift away from this question of 'how do we implement cognitive control' to 'how do we decide whether to recruit cognitive control?'. This is grounded in opportunity cost and expected value models of cognitive control [4,5••] as

well as work on striatal dopamine's role in reinforcement learning and motivation [6••]. It involves reframing the problem of cognitive control as a choice dilemma, shaped by learning mechanisms that serve to maximize reward and concurs with ideas that working memory allocation is value-based [7–9]. Addressing this will help us understand why we so often fail to (choose to) exert cognitive control, despite it being a cornerstone of human cognition.

To make these two key steps, this review begins to integrate hitherto separate lines of work on dopamine's role in cognitive control [10,11•] and dopamine's role in value-based decision-making [6••].

From static to dynamic cognitive states

The importance of persistence for cognitive control has received much attention across different cognitive research domains, including working memory [12•], selective top-down attention [13] and waiting for large rewards [14•]. For example, the predominant neurobiological model of working memory posits that stimulus information is stored via stable, elevated (persistent) activity within selective neurons [12•]. In line with this model, cognitive control is often argued to involve the active maintenance of patterns of persistent activity that represent current goals [15]. However, adequate control requires more than the active maintenance of, and focus on current goal representations. Our environment changes constantly. While writing this article, a fire might break out in the corridor behind me. To behave adaptively, I should allow my current goal representation (to finish this article) to be destabilized by new, unexpected inputs (the smell of smoke). Accordingly, there is increasing recognition that adequate cognitive control involves a dynamic adaptation of cognitive states, rather than merely persistent information processing.

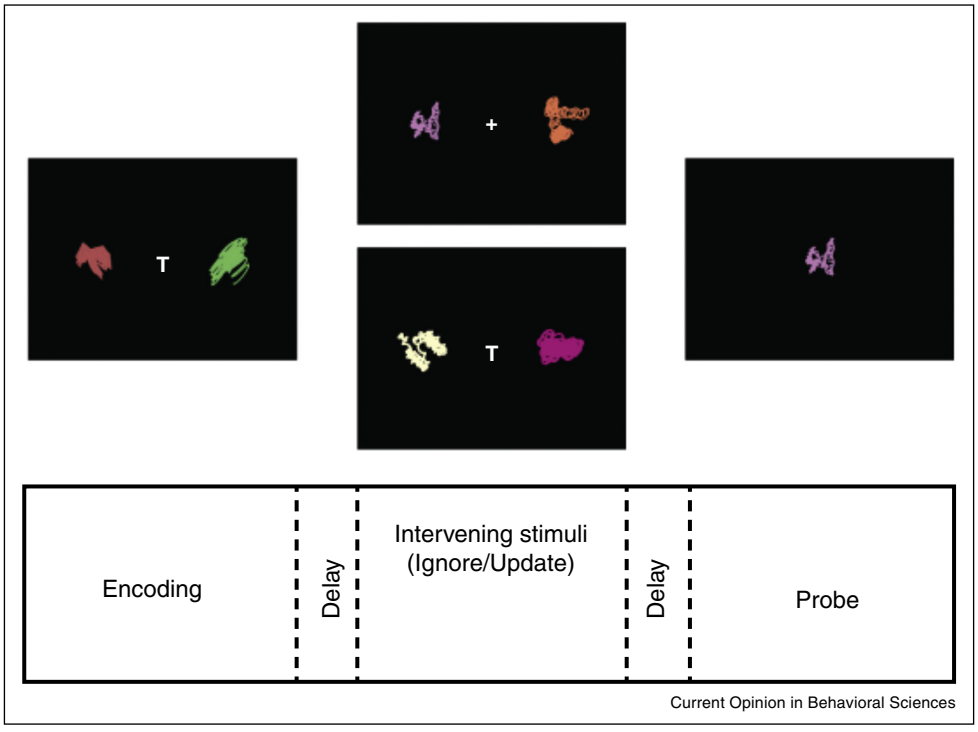
This development is paralleled by advances in the study of large-scale brain networks [16], where researchers have begun to recognize the benefits of variability and noise [17,18] and the value of mind wandering and task-unrelated thoughts [19]. Growing evidence indicates that large-scale brain networks are not stationary, but rather adapt dynamically over time [20]. Such time-dependent transitions between different network states might enable the brain to explore different functional configurations, reflecting its capacity to flexibly adapt to different contexts.

However, the mechanisms that drive these dynamic transitions and that arbitrate between such distinct brain states remain unknown. Biophysically realistic modelling work has led to dual-state theory, which assigns a key role to prefrontal dopamine [11•]. According to this theory, prefrontal cortex networks are either in a D1-dominated state, associated with intermediate levels of dopamine and characterized by a high energy barrier favouring robust stabilization of representations, or in a D2-dominated state, associated with suboptimal or supraoptimal levels of dopamine and characterized by a low energy barrier favouring fast flexible shifting between representations [11•]. A concrete prediction that arises from this theory is that dopaminergic drugs that optimize prefrontal dopamine (leading to intermediate rather than suboptimal or supraoptimal levels) might bias the system towards a stable state, good for goal-stabilization, but away from a flexible state, bad for goal-stabilization. Preliminary data from our lab can be captured by this dual-state framework and show that oral administration of the dopamine (and noradrenaline) transporter blocker methylphenidate (20 mg, acute) to healthy volunteers improves performance on a task requiring distractor-resistance of current working memory representations, while impairing performance on a well-matched task requiring flexible updating of current working memory representations (S Fallon *et al.*, unpublished data; Figure 1). These behavioural effects were accompanied by modulation of the prefrontal cortex, consistent with studies suggesting that prefrontal dopamine modulates the signal-to-noise ratio and the distractor-resistant maintenance of working memory patterns by acting on the prefrontal cortex [21•]. The signal-to-noise enhancing effects might be mediated by D1 receptor-dependent modulation of the distractor-resistance of delay-period activity in dorsolateral PFC [22]. Indeed increases in prefrontal dopamine D1 activity can potentiate the reliability of currently task-relevant responses [23•] and theoretical accounts highlight prefrontal dopamine's role in the precision of beliefs about the attainability of future goals [24]. Thus optimal levels of prefrontal dopamine seem key for the stabilization of current goal representations. Our preliminary data (Fallon *et al.*, unpublished data) suggest that this enhanced stabilization is accompanied, however, with performance impairment, when the current context requires goal-destabilization.

The potentiating effects of dopamine on the stabilization of current working memory representations in prefrontal cortex might incidentally also underlie the enhancing effects of dopaminergic medication in Parkinson's disease on goal-directed (as opposed to habitual) control of behaviour [25], which relies on the ability to keep online an explicit representation of the outcome (value) of behaviour [26]. In line with this observation, levodopa in healthy volunteers enhances model-based over model-free reinforcement learning in a sequential choice task [27], which also depends critically on working memory capacity [28] and explicit representations of the outcome (value) of behaviour [29].

However, the prefrontal cortex plays an important role, not just in the stabilizing aspects of cognitive control, but also, and perhaps primarily so, in the dynamic, adaptive aspects of cognitive control. Indeed, the prefrontal cortex

Figure 1



Schematic of the experimental paradigm employed to measure goal-stabilization and goal-destabilization [59]. Each trial consisted of an encoding period (two stimuli on either side of a 'T' for 'target'), a delay period and a probe period. Two novel stimuli were presented in the middle of the delay period. This delayed response task included two types of trials. On ignore trials, subjects had to ignore the intervening stimuli (not accompanied by a 'T'). On update trials subjects were instructed (using a 't' for 'target' presented simultaneously with the stimuli) to use these stimuli for updating working memory (displacing the original targets).

shows highly adaptive information coding, and is part of a network encoding multiple demands [30•,31••]. Dopamine has been argued to modulate such adaptive coding, in part by acting directly on the prefrontal cortex [32,33], for example by modulating short-term synaptic plasticity [31••] and/or biasing the system into a flexible D2 state [11•]. Nevertheless the mechanisms by which such adaptive coding is elicited remain unclear. Below I propose that dopamine in the striatum might play a complementary role to that of prefrontal dopamine.

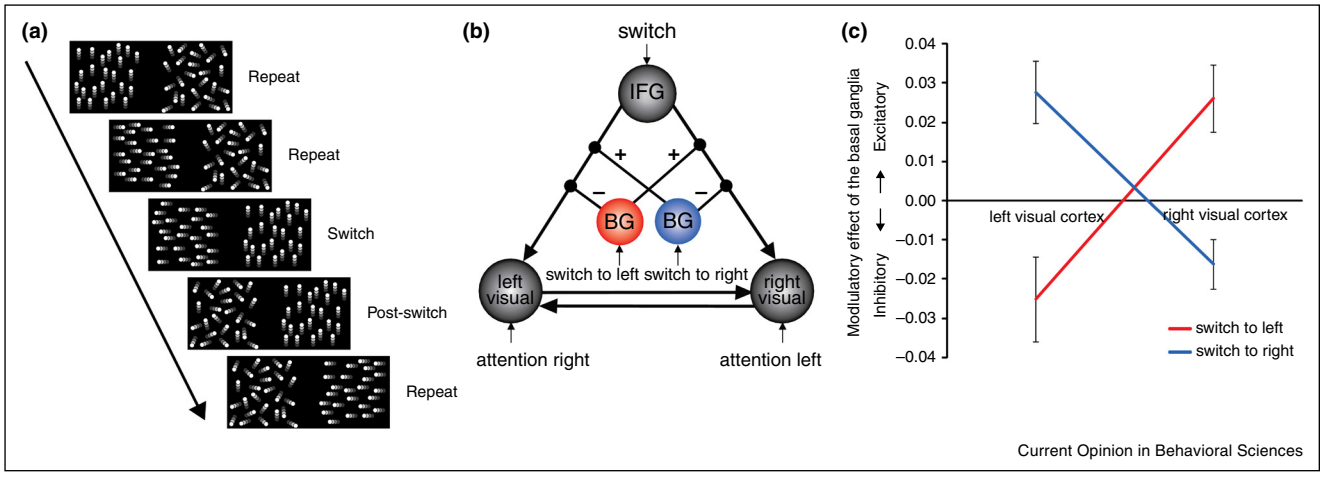
Striatal dopamine and flexible cognitive control

The prefrontal cortex does not act in isolation to elicit flexible adaptive control, but rather interacts with a set of deep brain subcortical structures, in particular the basal ganglia, in so-called fronto-striato-thalamo-frontal circuits to selectively gate both action as well as attention [34•,35,36]. Dopamine might well act through striato-thalamo-frontal circuitry to regulate information transmission between the prefrontal cortex and stimulus-specific regions in posterior cortex, depending on changing attention demands [34•,37•] (Figure 2), generally consistent with the recent proposal that subcortical systems gate the synchronization of neuronal populations across distinct cortical regions [38]. But how would the striatum know when to elicit flexible cortical gating, that is where to set the threshold for attention shifting? One possibility is that such dynamic gating is elicited by dopamine-dependent changes in the expected mental costs and benefits of cognitive control [4,8,35,39,40••].

Striatal dopamine and cost–benefit decision-making

Empirical data on the role of striatal dopamine are often grounded in theories about reinforcement learning and cost–benefit decision-making [6••]. In particular, tonic dopamine transmission in the striatum is thought to alter the threshold for allocating physical resources (energizing behaviour) and thus bias cost–benefit decision-making policies about whether to exert *physical* effort to obtain reward [6••,41–44]. One question for future work is whether analogous (striatal dopaminergic) mechanisms contribute to decision-making about *mental* effort [45,46]. This question is timely, given recent accounts that recast the problem of cognitive control in terms of a decision-making (or arbitration) problem, requiring integration of the expected payoff and mental effort cost of controlled

Figure 2



(a) Attention-switching paradigm used to assess striatal modulation of top-down attentional control [32]. Subjects were instructed to covertly attend to the left or right visual hemifield. On each trial (repeat trials), they had to discriminate the direction of a moving dot pattern at the attended side, while ignoring the unattended side (random noise). On switch trials, a moving dot pattern on the unattended side triggered a switch in attention. Subjects then continued performing the task on the opposite visual hemifield. **(b)** Non-linear dynamic causal modelling showed that BOLD data, acquired during the performance of this task, were consistent with a model, in which the striatum facilitates bottom up, salience-driven attentional shifts via modulation of top-down control of stimulus-specific regions in sensory cortex [34•]. Specifically, Bayesian model averaging showed that the basal ganglia both suppress previously attended visual information and enhance the newly attended visual information, via modulation of frontal top-down connections. **(c)** In line with this model, the basal ganglia inhibited connection strength with the left visual cortex when subjects switched attention to the left visual hemifield, but enhanced connection strength with the left visual cortex when subjects switched attention to the right visual hemifield. The opposite pattern was observed in the right visual cortex.
Adapted from Ref. [32].

processing, to determine whether to allocate cognitive control [4,39,40••,47,48]. If so, then failures of cognitive control (and related constructs, such as model-based learning) would not necessarily reflect a problem with the implementation of control, but might reflect mental demand avoidance [49••], a motivated choice-bias away from exerting mentally costly tasks, such as those involving cognitive control, and/or towards exerting mentally easy tasks.

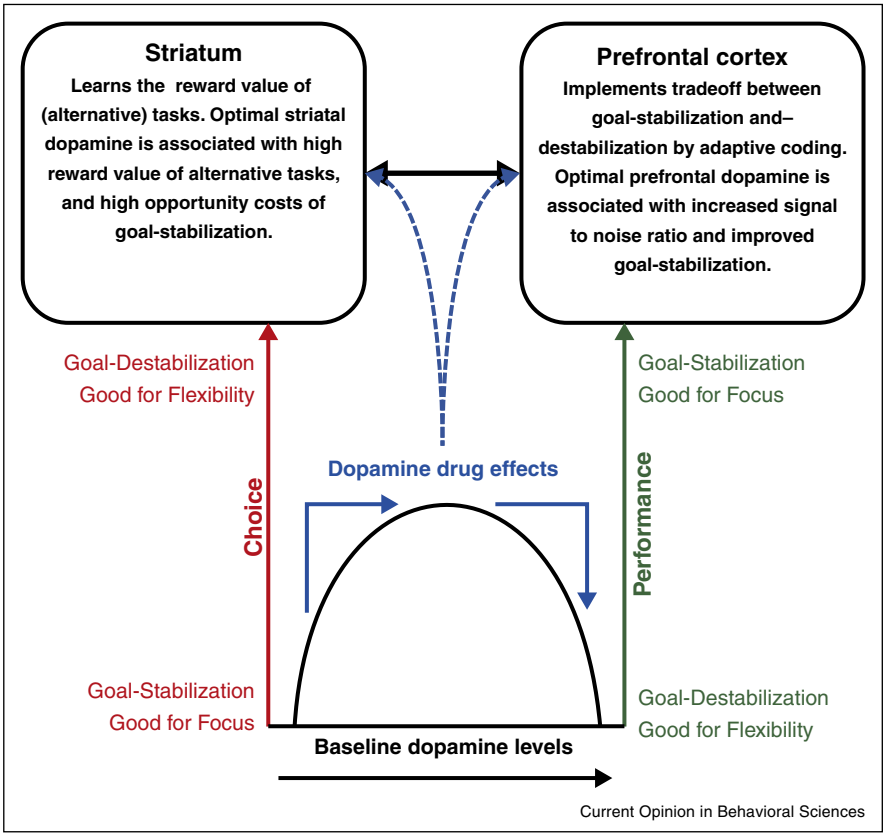
Dopamine and opportunity costs

According to recent opportunity cost theory of mental effort, the experience of mental effort, often accompanied by distractibility and mind-wandering, is proportional to an opportunity cost of persisting with the current task, equal to the foregone benefits of performing alternative tasks [5••]. These ideas are grounded in older motivational accounts of mental fatigue [50], and state that adequate performance of cognitive control tasks is costly, because they require focusing on current tasks, which interferes with performing rewarding alternative tasks. The experience of mental effort might then elicit the re-allocation of computational processes to more valuable alternatives, consistent with evidence that mental effort elicits flexible reconfiguration of intrinsic large-scale brain networks [51].

This position is reminiscent of the proposal that tonic dopamine promotes physically effortful response vigour by encoding the average net expected reward rate, a global, slowly changing term common to all the states and actions evaluated, which translates to the opportunity cost of wasted time, or sloth (and thus delaying future reward): the higher the level of tonic dopamine, the higher the expected reward rate, the more costly it is to delay motor responding [52,53•]. By analogy, the opportunity cost of mental effort might also be carried by tonic dopamine, with higher tonic dopamine corresponding to higher average expected reward rates of all available (including alternative) tasks and thus higher costs of the mentally effortful cognitive focusing state. These higher mental effort costs would then motivate destabilization of current goals and switching to alternative tasks. Mental effort might thus translate to a striatal dopamine-dependent motivational signal updating the trade-off between distinct cognitive states. One concrete hypothesis that arises from this proposal is that dopaminergic drugs that increase striatal dopamine might bias subjects away from choosing to perform effortful cognitive control tasks that require goal-stabilization (Figure 3).

To test this hypothesis, it will be necessary to objectively quantify the mental effort cost associated with different cognitive states involving goal-stabilization and goal-destabilization, as a function of the reward value of available tasks. In recent work on mental effort, neuroeconomic discounting procedures have been used to measure the

Figure 3



Working hypothesis. Dopaminergic drugs have distinct effects on cognitive control depending on the modulated target region. Dopaminergic drug effects are known to depend on baseline levels of dopamine, according to an inverted-U shaped relationship between dopamine and cognitive performance (not reviewed here, see Ref. [8]). Prefrontal dopamine is argued to affect the sharpening and stabilization of current goal representations. Conversely, striatal dopamine might act to bias cognitive control by modulating effort cost-based decision making about whether or not to exert cognitive control. Specifically, increases in striatal dopamine might be accompanied by enhanced average reward rate of all available (including alternative) tasks, thus motivating subjects to decide to avoid cognitively effortful computations such as goal-stabilization.

subjective value of mental effort by quantifying the extent to which effortful tasks cause subjects to discount monetary rewards [40••]. The use of such neuroeconomic procedures in combination with (pharmacological) neuroimaging techniques might enable us to investigate whether putative dopaminergic drug effects on the subjective cost/value of mental effort are mediated by drug effects on striatal dopamine. This approach will also allow us to test the complementary hypothesis, raised by various recent studies [4,48,54,55], that decision-making about mental effort also implicates frontal cortical regions, such as the anterior cingulate cortex, the anterior insula and the lateral frontal cortex.

The opportunity cost might also feature in another cornerstone of cognitive control, the capacity to delay gratification [14•,56]. In delay discounting paradigms, the opportunity cost is higher when subjects have to wait, while not doing anything else, than when being allowed to complete other activities during a delay preceding a large reward. Manipulating the opportunity cost of delay in delay gratification tasks can alter the discounting rate [57]. Administration of levodopa to healthy volunteers indeed increased impulsive choice of a small, immediate reward over a large, delayed reward by enhancing the diminishing influence of increasing delay on reward value (temporal discounting) and its corresponding neural representation in the striatum [58]. This result is consistent with the hypothesis that dopaminergic drugs can bias decision making away from prefrontal processes such as waiting for reward by acting in the striatum to enhance the cost of waiting and/or enhance the value of immediate action. Future work should elucidate the differences and similarities between mental effort and delay discounting.

Conclusion

Brain dopamine plays an important role in our ability to dynamically regulate the balance between opponent cognitive states, such as those involving goal-stabilization versus goal-destabilization, by adjusting processing in

circuits connecting the prefrontal cortex with the striatum. Specifically dopamine might promote goal-stabilization or goal-destabilization depending on the neural site of modulation. Optimal dopamine D1 receptor stimulation in prefrontal cortex promotes the stabilization of current goal representations by increasing the distractor-resistance, signal-to-noise ratio and/or reliability of these representations. Conversely, optimal levels of tonic dopamine in the striatum might bias value-based decision-making away from excessive goal-stabilization, by increasing its opportunity cost, which is equal to the net average expected reward rate associated not just with the current goal but also with available alternative goals. The functional opponency between goal-stabilization and goal-destabilization maps well onto the neurochemical reciprocity between dopamine in the prefrontal cortex and the striatum: Increases in prefrontal dopamine lead to decreases in striatal dopamine and vice versa. This observation incidentally also highlights the powerful self-regulatory capacities of the endogenous ascending neuromodulatory systems, a core function which might help the brain adapt itself to our ever changing environment. Whether we can potentiate this capacity of adaptive, dynamic cognitive control by external means, for example by enhancing dopamine (and noradrenaline) using dopaminergic (smart) drugs, remains an open question. The available evidence suggests instead that dopaminergic (smart) drugs bias the system towards one state at the expense of another, depending on demands for goal-stabilization and the neural (frontal versus striatal) region of drug action. Addressing this issue requires future work combining pharmacological neuroimaging with experimental paradigms that measure the dynamic balance between the oppponent cognitive states of goal-stabilization and goal-destabilization, as well as the ability to arbitrate between distinct cognitive states depending on task demands.

Conflict of interest

Nothing declared.

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- • of special interest
- •• of outstanding interest

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