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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