Overview

The costs and benefits of brain dopamine for cognitive control

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Cognitive control helps us attain our goals by resisting distraction and temptations. Dopaminergic drugs are well known to enhance cognitive control. However, there is great variability in the effects of dopaminergic drugs across different contexts, with beneficial effects on some tasks but detrimental effects on other tasks. The mechanisms underlying this variability across cognitive task demands remain unclear. I aim to elucidate this across-task variability in dopaminergic drug efficacy by going beyond classic models that emphasize the importance of dopamine in the prefrontal cortex for cognitive control and working memory. To this end, I build on recent advances in cognitive neuroscience that highlight a role for dopamine in cost–benefit decision making. Specifically, I reconceptualize 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 an ill-defined term but can be broadly defined 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 a hallmark of human cognition.[1] Yet 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. Thus, it is not surprising that many of us crave control and focus: We do not value being distracted or impulsive, we emphasize the costs of multitasking,[2,3] and we consider failures of focus and mind wandering as resulting from sloppiness and leading to wasting of resources, at least in most work-related environments. Yet, this emphasis on cognitive focus does not chime with society's need for creative innovation, which requires a balance between focus and flexibility.[4]

Our craving of focus and control is evident from our tendency to enhance it beyond optimal, for example, using medication that increases dopamine and noradrenaline, such as methylphenidate and modafinil. Drugs like methylphenidate, which act by blocking the dopamine (noradrenaline) transporter, are used to combat cognitive and motivational control deficits, seen in disorders like AD(H)D, but are also increasingly used by healthy people for cognitive enhancement, such as smart pills.[5,6] Estimates of the proportion of healthy students using drugs like methylphenidate off-label range from 4 to 16%.[7,8] The problem is that smart drugs do not help everyone in every context. Catecholaminergic drug effects vary greatly across individuals and tasks, with some individuals and tasks being impaired rather than improved.[9] Resolving the large variability in catecholaminergic drug effects across individuals and contexts is a key scientific puzzle and requires an understanding of the neurocognitive mechanisms by which dopamine and noradrenaline alter cognitive

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control. Progress in such understanding will be important, not just for preventing failures of cognitive control but also for minimizing the costs of too much cognitive control. Moreover, it will enable us to predict who will benefit from catecholaminergic drugs in which cognitive context, thus having considerable implications for the use of cognitive enhancers that act on the catecholamine system.

This paper begins to address these issues by studying the large within-subject variability in the effects of dopamine across distinct task demands. The existence of large variability across different individuals is addressed elsewhere,[9,10] as is the role of noradrenaline[11–13] and the other major ascending neuromodulatory systems,[14] which are known to play a complementary role to dopamine in flexible cognitive control. The present review speaks most readily to the cognitive control of working memory and attention rather than to the control of action, although various of the constructs discussed below are relevant for understanding the modulation of action control.[15]

The first step towards progress in our understanding of dopamine's role in cognitive control involves a redefinition of cognitive control that extends beyond the common emphasis on the ability to maintain, focus, and stabilize current goal representations. Adaptive behavior depends not just on cognitive focus and stabilization but requires a dynamic equilibrium between the distinct cognitive actions of (i) goal stabilization,[a] defined here as the ability to actively maintain and protect from distraction current goal representations, and (ii) goal destabilization, defined here as the ability to allow new input to alter current goal representations. Accumulating evidence indicates that brain dopamine plays an important role in this ability to dynamically regulate the balance between goal stabilization and goal destabilization by adjusting processing in circuits connecting the prefrontal cortex with the striatum.[9,16]

The next question is how we arbitrate between these different cognitive actions of goal stabilization and goal destabilization.[b] To this end, the second step in this review involves reconceptualizing cognitive control as a cost-/benefit-based decision instead of solely an implementation challenge.[15,17,20] Classic prefrontal models of cognitive control primarily address our ability to implement control.[21] 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?'.[15,20,22–24] This shift is grounded in opportunity cost and expected value models of cognitive control[17,19] as well as work on striatal dopamine's role in reinforcement learning and motivation.[25,26] It involves reframing the problem of cognitive control as a choice dilemma, shaped by learning mechanisms that serve to maximize reward. It concurs with ideas that working memory allocation is value-based[27–29] and reconciles literatures on dopamine, cost–benefit decision making, and cognitive control. Addressing this issue will bring us closer to understanding why we so often fail to (choose to) exert cognitive control, despite it being a cornerstone of human cognition.

To perform these two key steps, this review begins to integrate hitherto separated lines of work on the role of dopamine in cognitive control[9,30] and that in learning and decision making.[25,26,31]

FROM COGNITIVE STABILITY TO COGNITIVE LABILITY

The importance of persistence for cognitive control has received much attention across different cognitive research domains, including working memory,[32,33] selective top–down attention,[34,35] and waiting for large rewards.[36] For example, the predominant neurobiological model of working memory posits that stimulus information is stored via stable, elevated (persistent) activity within selective neurons.[33] In line with this model, cognitive control is often argued to involve the active maintenance of patterns of persistent activity that represent current goals.[21] However, adequate control requires more than the active maintenance of, and focus on, current goal representations. Our environment changes constantly. To this end, our minds should allow current goal representations to be destabilized by new, unexpected inputs, for example by allowing such inputs to attract bottom-up attention. While meeting with my colleagues to discuss a project, a small fire might break out in the corridor behind me. Adaptive behavior requires my current goal representations to be destabilized by the new, unexpected input of the smell of smoke. Accordingly, what we need is a dynamic equilibrium between goal stabilization and goal destabilization.

Prefrontal Dopamine and Cognitive Stability

There is strong empirical evidence for the role of dopamine in the prefrontal cortex in the stabilization of current goal representations in working memory. A wealth of studies with experimental animals and computational modeling indicates that dopamine potentiates the maintenance of patterns of neuronal firing in widespread regions of prefrontal cortex,[37–39]

presumably by D1 receptor-dependent modulation of delay-period activity in the dorsolateral prefrontal cortex[40,41]. For example, neurophysiological data from monkeys showed that D1 receptor stimulation in the nonhuman primate prefrontal cortex improves the spatial tuning of cells during the performance of a spatial delayed response task by blocking task-irrelevant firing, thus sculpting current goal representations.[42] Indeed, administration of the dopamine receptor agonist bromocriptine to healthy volunteers was shown to alter distractor resistance on a delayed response task of working memory[43] and to increase neural signaling in the prefrontal cortex during distractor resistance[44]. Critically, individual differences in the dopaminergic drug effects on distractor resistance were found to correlate with drug effects on delay period signal in the prefrontal cortex, as well as on functional connectivity between the prefrontal cortex and stimulus-specific regions in the posterior visual association cortex.[43]

The potentiating effects of prefrontal dopamine on the distractor resistance of current working memory representations in prefrontal cortex might also contribute to the enhancing effects of dopaminergic medication in Parkinson's disease on goal-directed (over habitual) control of behavior,[47,48] which relies on the ability to maintain online an explicit representation of the (route to the) outcome of behavior. Indeed, infusions of dopamine into the prefrontal cortex restored outcome sensitivity in experimental animals, putatively by engaging attentional/working memory processes[49]. This finding concurs with results showing that administration of levodopa to healthy volunteers enhances model-based over model-free reinforcement learning on a sequential choice task,[50] which also depends critically on working memory capacity[51] and explicit representations of the outcome (value) of behavior.[52] Indeed, both model-based choice and working memory capacity could be predicted from individual differences in dopamine synthesis capacity (measured in the striatum but presumably covarying strongly with prefrontal dopamine levels).[53,54]

Critically, the molecular mechanisms in prefrontal cortex that sculpt and stabilize current working memory representations might well confer vulnerability when the current task demands mental flexibility.[10,55] Indeed, prefrontal dopamine depletion in nonhuman primates elicits not only impaired attentional set maintenance[45] but also enhanced attentional set shifting.[56] Such findings can be reconciled with the dual-state theory of prefrontal dopamine functioning. According to this theory, which was based on biophysically realistic modeling work, prefrontal cortex networks are either in a D1-dominated state, associated with intermediate levels of dopamine and characterized by a high energy barrier favoring 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 favoring fast flexible shifting between representations.[30] 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 cognitive state, good for goal stabilization, but away from a flexible cognitive state, good for goal destabilization. Preliminary work from our lab can be interpreted in the context of this dual-state framework and show that oral administration of the dopamine (and noradrenaline) blocker methylphenidate (20 mg, acute) to healthy volunteers improves performance on a task that required distractor resistance of current working memory representations while impairing performance on a well-matched task that instead required flexible updating of current working memory representations.[57] These behavioral effects were accompanied by modulation of the prefrontal cortex, in line with studies implicating prefrontal dopamine in the distractor resistance and stabilization of current goal representations with high signal-to-noise ratio. These data demonstrate that an increase in such stabilization is accompanied, however, by impairment when the task requires goal destabilization.

Of course, 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.[58,59] The prefrontal cortex shows highly adaptive information coding and is part of a network encoding multiple demands.[60] Neuronal populations in the prefrontal cortex exhibit widespread reallocation of prefrontal processing resources as an attentional focus is established,[61] and neural tuning profiles in the prefrontal cortex adapt to accommodate changes in behavioral context.[62] Furthermore, functional MRI work has found that the brain-wide functional connectivity pattern of the prefrontal cortex (and parietal cortex), thought to be key for facilitating the ability to implement cognitive control, shifted more than those of other networks across a variety of task states, suggesting that the prefrontal cortex serves as a flexible hub for adaptive cognitive control.[63]

It is likely that dopamine acts in part directly on the prefrontal cortex to elicit adaptive dynamics of cognitive control,[30,55,64–67] for example, by modulating short-term synaptic plasticity.[62] In this context, it is interesting to note that stress can impair performance on tasks that require stable working memory

representations,[51,68] perhaps by eliciting supraoptimal stimulation of dopamine D1 receptors that sculpts network inputs to refine working memory representations and by biasing the system into a more flexible D2 state.[30] Increases in prefrontal catecholamine transmission, elicited for example by stress, can indeed trigger coordinated, brain-wide shifts in neural functioning that enable us to reallocate processing resources to meet unstable task demands.[69] However, the mechanisms by which such adaptive coding is elicited remain unclear. In the following sections, I propose that dopamine in the striatum might play a complementary role to that of prefrontal dopamine.

Striatal Dopamine and Cognitive Lability

The prefrontal cortex does not act in isolation to bias cognitive control but rather interacts with a set of deep brain subcortical structures, particularly the basal ganglia, in so-called fronto-striato-thalamo-frontal circuits.[29,70] For example, dopamine might well act via the striatum through such striato-frontal circuitry to modify goal stabilization by gating new inputs into the prefrontal cortex, thus destabilizating current working memory representations and eliciting a form of cognitive lability.[71] Indeed, accumulating evidence indicates that striatal dopamine plays a key role in attentional gating or shifting in response to unexpected, behaviorally important stimuli.[9,16,72] For example, recent dynamic causal modeling of functional neuroimaging data[73] has shown that the basal ganglia guided bottom–up attention shifts by focally releasing inhibition of task-relevant representations while simultaneously inhibiting task-irrelevant representations in the posterior stimulus-specific cortex by selectively modulating prefrontal top–down connections to this posterior stimulus-specific cortex.[73] Of note is the fact that the attention shifts in this paradigm were elicited in a bottom–up manner by salient stimuli, rather than by instruction. As such, the effects reflect modulation of bottom–up attentional reorienting, which is a form of cognitive lability, rather than that of top–down attentional control, and concur with the observation that unexpected stimuli that are behaviorally significant have the capacity to elicit firing of dopaminergic neurons.[72] Subsequent work using the same paradigm showed effects of the dopaminergic D2 receptor drug bromocriptine on neural signals in the basal ganglia as well as functional connectivity between the basal ganglia and the prefrontal cortex in a manner that depended on individual differences in striato-thalamo-frontal white matter tracts.[74] These data suggest that dopamine might act through striato-thalamo-frontal circuitry to bias attention shifting by regulating information transmission between the prefrontal cortex and stimulus-specific regions in the posterior cortex. This observation concurs generally with the proposal that subcortical regions regulate selective attention mechanisms that route behaviorally relevant information through large-scale cortical networks, perhaps by gating the synchronization of neuronal populations across distinct cortical regions.[75]

Together, these data raise the hypothesis that dopamine elicits flexible reorienting of attention by acting on subcortical structures, such as the striatum. The question remains how the striatum would know when to allow such reorienting of attention, that is, where to set the threshold for attention shifting. One possibility is that such attentional reorienting is elicited by dopamine-dependent changes in the mental costs and benefits of effortful goal stabilization.[19,20,22,28,76] Thus, the mechanism by which dopamine elicits attention shifting might entail modulation by dopamine of decision making based on the costs and benefits of goal stabilization.

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.[25,31] Current views emphasize a role for phasic striatal dopamine in reward and model-free reinforcement learning, where it serves as an instrumental teaching signal to update expectations based on past rewards via the coding of a temporal difference reward prediction error.[77,78] In keeping with this line of thinking, dopaminergic medication in a range of human patient groups as well as healthy (young and old) volunteers was shown to potentiate learning from, and choice based on, reward and/or reward prediction error coding in the striatum[79] and, in fact, to impair learning from punishment[80,81] in a manner consistent with modulation of phasic dopamine signaling in the striatum.[82,83]

A different computation might be carried by tonic dopamine transmission in the striatum.[84] While the phasic dopamine response is known to correspond to the reward prediction error, tonic dopamine might correspond instead to the net average reward rate, which serves as a baseline against which to compare the obtained rewards (and punishments).[85] Unlike phasic dopamine, tonic dopamine contributes to processes involving the exertion and perception of effort, such as behavioral energization and Pavlovian

to instrumental transfer.[85–91] Animal models of effort cost-based decision making overwhelmingly implicate mesolimbic dopamine in our willingness to exert effort for a larger reward,[92–94] and this is supported by recent work with human volunteers, which also implicates dopamine in effort-based decision making.[95,96] The animal models particularly implicate the ventral striatum, with ventral striatal dopamine acting on medium-sized spiny neurons to modulate converging information originating from connected frontal cortical regions, such as the anterior cingulate cortex.[93] By this means, dopamine is thought to alter the threshold for allocating physical resources (energetic responses) and thus bias cost–benefit decision making policies about physical effort. The obvious next question is whether analogous (striatal dopaminergic) mechanisms might contribute to decision making based on *mental* effort. Recent data indeed indicate that the same ventral striatum region qualifies as a common motivational node, driving both cognitive and motor brain regions during the exertion of mental and physical effort, respectively.[97,98] Furthermore, as is the case for physical effort, catecholaminergic psychostimulants, such as amphetamine and caffeine, also alter decision making based on mental effort.[99,100,c]

Elucidating dopamine's role in decision making based on mental effort is pertinent given recent accounts that recast the problem of cognitive control in terms of a decision-making problem, requiring integration of the expected payoff and mental effort cost of controlled processing to determine whether to allocate cognitive control.[15,17,19,20,22,76,101–103] One implication of this hypothesis is that failures of cognitive control do not necessarily reflect a problem with the implementation of control but might reflect mental demand avoidance.[24,104,105] Thus, cognitive control failures might result from a motivated choice bias away from exerting mentally costly tasks, such as those involving goal stabilization.[76]

Dopamine and Opportunity Costs

According to the recent opportunity cost hypothesis of mental effort, cognitive demand avoidance is a function of a mental opportunity cost that is equal to the reward value of performing the next best alternative task.[17] In this framework, the experience of mental effort, which is often accompanied by increased distractibility and goal destabilization, is argued to correspond to an opportunity cost of persistence with the current task, equal to the foregone benefits of performing alternative tasks, such as mind wandering. According to this hypothesis, performance of cognitive control tasks is costly because it requires goal stabilization, persistence, and focus on current tasks, which interfere with performing rewarding alternative tasks.

Such opportunity cost accounts of meta-decisions about cognitive control[15] are reminiscent of opportunity cost accounts of physical effort,[85] according to which tonic dopamine, which corresponds to the average net expected reward rate, translates to the opportunity cost of wasted time or delaying future reward: the higher the level of tonic dopamine, the higher the rate, the more costly it is not to respond.[85] This opportunity cost model of response vigor (physical effort) accounts for the large body of evidence from work with experimental animals showing effects of tonic dopamine manipulations on behavioral vigor (response rate), energization, Pavlovian biases as well as effort-based choice.[89,91,93,94] Moreover, levodopa-induced changes in the net expected reward rate were shown to account for effects of levodopa on response vigor on a simple choice task in healthy human volunteers[106]: Levodopa enhanced response vigor as a function of increasing average reward rate.

In the opportunity cost model of physical effort, the net average expected reward rate is a global, slowly changing term common to all the states and to all actions and rates evaluated, corresponding to tonic levels of dopamine in the striatum. By analogy, the opportunity cost of mental effort might also be carried by tonic striatal dopamine, with higher tonic dopamine in the striatum corresponding to higher average expected reward rates of all available (including alternative) tasks and perhaps higher mental effort costs of the focusing state. Such higher mental effort costs of focusing would then motivate switching to alternative tasks. Mental effort might thus translate to a striatal dopamine-dependent motivational signal for goal destabilization and attentional reorienting. Indeed, the experience of mental effort has long been accepted to serve to motivate flexible, adaptive behavior[107,108] by eliciting the reallocation of computational processes to more valuable alternatives, a hypothesis that concurs with evidence that mental effort elicits a dynamic reconfiguration of intrinsic large-scale brain networks.[109] Thus, mental effort might well serve as a striatal dopamine-dependent motivational signal to update the trade-off between the cognitive actions of goal stabilization and goal destabilization. One prediction that arises from this proposal is that dopaminergic drugs that increase striatal dopamine bias subjects away from choosing to perform effortful cognitive control tasks that require persistence with and stabilization of the

current goal while biasing their system toward a cognitive state that optimizes goal destabilization.

A key question for ongoing work is whether the avoidance of mentally effortful tasks is best accounted for by an opportunity cost that corresponds to the reward value of the next best alternative,[17] or rather by average reward rate, as proposed by Boureau et al.[15] To assess this, it will be necessary to objectively quantify the mental effort cost associated with different cognitive modes of goal stabilization and goal destabilization as a function of the reward value of alternative task performance as well as of average reward value (see also Ref 110). In recent work on mental effort, neuroeconomic discounting procedures have been used to measure the subjective value of mental effort by quantifying the extent to which tasks cause subjects to discount monetary rewards.[76,111] In this work, subjects completed a decision-making task involving choices between two tasks for money. The use of such neuroeconomic procedures in combination with (chemical and 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.

Dopamine and Intertemporal Choice

Of interest in this context is the recent observation that another cornerstone of cognitive control, that is, the capacity to delay gratification, depends critically on the opportunity cost of waiting.[112] This opportunity cost of delay depends on limitations placed on activities until receipt of the outcome. It is higher when subjects have to wait, while not doing anything else (cf. waiting in line) than when being allowed free to complete other tasks during the delay to the large reward. Indeed manipulating the opportunity cost associated with tasks of delay gratification, for example, by self-distraction or by having each choice affect the time remaining for later trials, altered the discounting rate in humans and nonhuman primates.[112] Intriguingly, administration of levodopa to healthy volunteers who performed an intertemporal choice task was shown to increase impulsive choice for the small, immediate over the large, delayed reward by enhancing the diminishing influence of increasing delay on reward value (temporal discounting) and its corresponding neural representation in the striatum.[113] This result is consistent with the hypothesis that dopaminergic drugs bias decision making away from prefrontal processes, such as waiting for reward, by acting in the striatum to enhance the cost of waiting. The observation that opportunity costs might contribute to performance across tasks of delay and mental effort discounting does raise the question whether costs of goal stabilization and focus correspond more readily to time costs rather than energetic effort costs. It is possible that the cost of focusing and suppressing distractions increases with increasing time as alternative opportunities accumulate. More research is needed to elucidate the differences/similarities between mental effort and time discounting.

Dopamine and Pavlovian Control

Another open question to be assessed in future (computational) neuroimaging work is whether effects of dopamine on Pavlovian behaviors can also be accounted for by modulation of an opportunity cost that is equal to the average expected reward rate, presumably at the level of the striatum.[85,114] Pavlovian biases represent stereotyped hard-wired behavioral responses to the occurrence of affectively important outcomes or learned predictions of those outcomes so that, under Pavlovian control, vigor and valence are coupled, with reward eliciting approach and activation. Dopamine has been shown to potentiate appetitive Pavlovian biases in experimental animals[86–88,91,115] and human volunteers,[116] and effects of levodopa in humans on various behavioral paradigms can be explained by modulation of appetitive Pavlovian biasing.[117,118] Future computational neuroimaging work might attempt to elucidate the neurocomputational basis of these effects in terms of increased average reward rate and striatal opportunity costs. Alternatively, when Pavlovian biases compete with instrumentally appropriate responses, dopamine might act directly in the prefrontal cortex, as we have seen in the context of working memory, to potentiate the sculpting and stability of currently relevant, instrumental outcome representations, thus helping subjects overcome competing Pavlovian biases (Ref 119 p. 2012; Ref 120). Future work should disentangle whether apparently paradoxical effects of dopaminergic drugs on paradigms in which Pavlovian biases compete with instrumentally appropriate responses can be accounted for by modulation of distinct prefrontal and striatal brain regions. One speculative possibility is that, in such contexts, dopamine-induced potentiation of instrumentally appropriate, goal-directed behavior[119,120] reflects expression of the stabilizing effects of prefrontal dopamine on current goal representations[121] (or their downstream consequences for dorsomedial striatal model-free representations). Conversely, dopamine-induced potentiation of Pavlovian biases[86–88] might reflect increases in ventral striatal dopamine through

increases in the opportunity costs of time and/or goal stabilization.

Dopamine and Incentive Motivation

Recasting the problem of cognitive control in terms of a striatal dopamine-dependent decision problem, which is a function of the opportunity cost of goal stabilization, helps us address longstanding questions about the motivational enhancement of cognitive control.[22,122] In folk psychological terms, being motivated implies being goal-driven. Accordingly, one might intuit that motivation just has beneficial consequences for our ability to direct our behavior at our cognitive goals. In line with this intuition, appetitive motivation—the state triggered by external stimuli that have rewarding properties—has been argued to have enhancing effects on cognitive control.[122] Indeed, reward motivation was recently shown to improve the discriminability of task-relevant information coded and maintained in frontoparietal brain regions.[123] However, much evidence indicates that incentive motivation does not enhance all cognitive processes in a nonspecific manner, leaves various cognitive processes unaffected, and can in fact impair some cognitive processes. For example, we have argued that appetitive motivation, which is known to implicate changes in dopaminergic activity, has functionally selective consequences for cognitive control.[124] Thus, effects of appetitive motivation (elicited by the promise of reward) on striatal neural signaling were accompanied by selective potentiation of the ability to switch between different tasks consistent with the hypothesis that striatal dopamine promotes goal destabilization. However, appetitive motivation had detrimental consequences for a different form of cognitive control: The promise of reward interfered with the ability to proactively focus on goal-relevant information and to ignore irrelevant information.[124] Subsequent work has shown that Stroop interference control was particularly impaired by incentive motivation in subjects who already have high baseline levels of striatal dopamine synthesis capacity.[125] The finding that appetitive motivation can impair cognitive control and focus while enhancing cognitive switching by acting on striatal dopamine is fully expected in the current framework of dopamine's opportunity costs.[31] If we conceptualize incentive motivation as an increase in the average expected reward rate associated with all available (current and alternative) tasks, then it should also lead to an increase in the opportunity cost of control tasks that require goal stabilization and focus, thus promoting a shift away from cognitive focusing towards goal destabilization and cognitive switching in a striatal dopamine-dependent manner. Thus, as is the case for dopamine, appetitive motivation likely has contrasting effects on goal stabilization versus goal destabilization depending on whether it acts on the prefrontal cortex or in the striatum. This, in turn, will likely depend on the baseline levels of dopamine in these distinct brain regions.[9]

CONCLUSION

Progress in our understanding of dopamine's role in cognitive control requires two key steps. First, it depends on recognition that adaptive cognitive control requires a demand-dependent equilibrium between goal stabilization and goal destabilization. Second, it requires reconceptualizing cognitive control as a cost–benefit decision instead of solely an implementation challenge. To this end, we should begin to integrate hitherto separated lines of work on dopamine's role in cognitive control and dopamine's role in cost–benefit decision making. These lines of work indicate that brain dopamine plays an important role in our ability to dynamically regulate the balance between goal stabilization and goal destabilization by adjusting processing in circuits connecting the prefrontal cortex with the striatum. Specifically, dopamine might promote cognitive stabilization or destabilization depending on the neural site of modulation. Optimal dopamine D1 receptor stimulation in the prefrontal cortex is hypothesized to promote the stabilization of current goal representations by increasing the distractor resistance of these representations. Conversely, optimal levels of tonic dopamine in the (ventral) striatum are hypothesized to bias value-based decision making away from current goal stabilization by increasing its opportunity cost, equal to either the value of the next best alternative task or the average reward rate. The functional opponency between cognitive stabilization and goal destabilization maps well onto the neurochemical reciprocity between dopamine in the prefrontal cortex and the striatum; increases and decreases in prefrontal dopamine lead to decreases and increases in striatal dopamine, respectively.

The proposal that prefrontal dopamine and striatal dopamine act in opposite directions concurs with the well-known neuroanatomical specificity of dopamine's actions and builds on work with experimental animals that allows local manipulations of dopamine in selective brain regions.[45] Importantly, it might well account for many apparently paradoxical effects of dopamine in humans. For example, administration of levodopa can boost model-based reasoning in

cognitive tasks, giving rise to presbyobic behavior, perhaps by acting on the prefrontal cortex, while also boosting impulsivity in delayed gratification tasks, giving rise to myopic behavior, perhaps by acting on the striatum. Of course, this example also highlights the complexity of the effects of systemic dopamine manipulations, which act on both the prefrontal cortex and the striatum, as well as the complexity of making predictions about such effects. Indeed, I have argued that the target region of dopamine does not act alone in determining its effect. Rather, as reviewed extensively elsewhere, the effects of dopamine depend also on individual differences in the baseline level of dopamine in that target region.[9] It is the interaction between these features of dopamine and its neuroanatomical specificity as well as its baseline sensitivity that together determine its effect. Specifically, dopaminergic drugs are predicted to boost goal stabilization in subjects with low baseline dopamine levels in the prefrontal cortex, while these same drugs are predicted to boost goal destabilization in subjects with low baseline dopamine levels in the striatum. Consistent with these hypotheses is the observation that dopaminergic drugs have remarkably distinct effects in patients with mild Parkinson's disease, where they can enhance distractibility,[126] and in patients with ADHD, where they reduce distractibility. This is less surprising if we take into account evidence that Parkinson's disease is characterized by severe dopamine depletion in the striatum but relatively unaffected dopamine levels in the prefrontal cortex,[127] while ADHD is rather characteristically accompanied by catecholamine depletion in the prefrontal cortex. Indeed, drugs like levodopa and dopamine receptor agonists are thought to act primarily in the striatum in patients with Parkinson's disease,[128] while the cognitive effects of low-dose psychostimulant drugs like methylphenidate have been attributed primarily to action on the prefrontal cortex.[129,130] In short, dopaminergic drugs likely boost the functioning of brain regions with low baseline levels of dopamine more readily than that of brain regions with already optimized dopamine levels.

One might argue that the proposal that dopamine's actions depend on these two interactive factors renders explanations too easy and predictions too difficult. Indeed, I fully recognize that, to provide definitive evidence for the present proposal, we need to combine the use of fMRI, to assess the neural locus of dopamine's effects during task processing, with neurochemical PET, to assess individual differences in the baseline level of dopamine in those neural loci.

The existence of neurochemical reciprocity between dopamine in the prefrontal cortex and the striatum incidentally also highlights the powerful self-regulatory capacities of the endogenous ascending neuromodulatory systems, a core function of which might be to help the brain adapt itself to our ever changing environment. Whether we can potentiate this capacity of dynamic cognitive control by external means, for example, by enhancing dopamine (and noradrenaline) using smart pills such as methylphenidate, or by non-pharmacological means, such as mindfulness training or extrinsic motivation, remains an open question. Addressing this requires future work to combine pharmacological and/or chemical neuroimaging with experimental paradigms for measuring arbitration between distinct cognitive states of goal stabilization and goal destabilization. Existing evidence suggests, in contrast, that current means of enhancement (through dopamine and other means) bias the system towards one cognitive state at the expense of the other, in fact paradoxically interfering with dynamic cognitive control. For example, administration of a clinically relevant oral dose of 20 mg of the dopamine (and noradrenaline) transporter blocker methylphenidate to healthy people was shown to increase cognitive focus and distractor resistance of current working memory while impairing the flexible updating of those representations.[57] Thus, methylphenidate had diametrically opposite effects within the same people on the ability to ignore and update current working memory representations. This is not surprising given that a bias toward one cognitive state, such as goal stabilization, is often paired, sometimes by definition, with a bias away from the other, antagonistic state, such as goal destabilization. The implication of this observation is that the use of catecholaminergic drugs like methylphenidate should be tailored to the task context, thus impeaching its potential as an enhancer of true dynamic cognitive control.

NOTES

[a] This distinction is closely related to that between top-down and bottom-up attention.

[b] In other words, how does our brain set the threshold for allowing new, unexpected input to attract bottom-up attention and to impact current goal representations?

[c] There are also good reasons for doubting that all effort is unitary, not least because the metabolic determinants of physical effort might have no analogue in mental effort.[17,76] Future work is needed to elucidate the differences between mental and physical effort.

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