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Methylphenidate boosts choices of mental labor over leisure depending on striatal dopamine synthesis capacity

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The cognitive enhancing effects of methylphenidate are well established, but the mechanisms remain unclear. We recently demonstrated that methylphenidate boosts cognitive motivation by enhancing the weight on the benefits of a cognitive task in a manner that depended on striatal dopamine. Here, we considered the complementary hypothesis that methylphenidate might also act by changing the weight on the opportunity cost of a cognitive task, that is, the cost of foregoing alternative opportunity. To this end, 50 healthy participants (25 women) completed a novel cognitive effort-discounting task that required choices between task and leisure. They were tested on methylphenidate, placebo, as well as the selective D2-receptor agent sulpiride, the latter to strengthen inference about dopamine receptor selectivity of methylphenidate's effects. Furthermore, they also underwent an [^{18}F]DOPA PET scan to quantify striatal dopamine synthesis capacity. Methylphenidate boosted choices of cognitive effort over leisure across the group, and this effect was greatest in participants with more striatal dopamine synthesis capacity. The effects of sulpiride did not reach significance. This study strengthens the motivational account of methylphenidate's effects on cognition, and suggests that methylphenidate reduces the cost of mental labor by increasing striatal dopamine.

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INTRODUCTION

The brain catecholamines have long been implicated in a wide range of cognitive functions, including working memory and cognitive control [1–3]. Drugs altering catecholamine transmission are first-line treatment for disorders accompanied by deficits in working memory and cognitive control, such as attention deficit/hyperactivity disorder (ADHD) [4, 5], and are commonly used for cognitive enhancement in healthy people [6–8]. Various studies have demonstrated that acute administration of psychostimulants, like the dopamine and noradrenaline transporter blocker methylphenidate, enhances working memory and cognitive control, and decreases feelings of fatigue in healthy individuals [9–16].

Such cognitive effects of catecholaminergic drugs have been most commonly attributed to a modulation of the ability to implement cognitive control, often associated with the prefrontal cortex [1]. However, recent progress suggests that cognitive control might also be altered by changing motivation, that is the willingness to engage with a cognitive task, rather than ability alone [17, 18]. Specifically, we have posited that the cognitive enhancing effects of drugs like methylphenidate, which act by blocking the dopamine and noradrenaline transporters, reflect changes in cost/benefit-based decision-making about cognitive control, elicited by striatal dopamine [19, 20]. While prior evidence, for example, from medication withdrawal studies in Parkinson's disease, generally concurred with this hypothesis [18, 21–23] (but see [24]), there was, until recently, no direct evidence for a specific role for dopamine in the striatum. To definitively test this role for striatal dopamine in cognitive motivation, we set up two separate cognitive effort discounting experiments in the context of a large pharmacological PET study, with 100 healthy volunteers. In this study, we directly quantified striatal dopamine synthesis capacity with PET, while also measuring effects of methylphenidate and sulpiride. In both experiments, participants completed a working memory task prior to drug administration and a cognitive effort discounting task after drug administration, allowing us to isolate drug effects on motivation in a manner that was not confounded by drug effects on performance. In a separate session, participants underwent an [^{18}F]DOPA PET scan to quantify dopamine synthesis capacity. Uptake of the radiotracer [^{18}F]DOPA indexes the degree to which dopamine is synthesized in (the terminals of) midbrain dopamine neurons, providing a relatively stable trait index of dopamine transmission that is less sensitive to state-dependent changes in dopamine levels [25] (but see [26]) than other dopamine PET tracers, such as [^{11}C]raclopride or [^{18}F]fallypride, which reflect D2/3-receptor availability. To substantiate the hypothesis that the effects of the nonspecific catecholamine enhancer methylphenidate (which increases both dopamine and noradrenaline in both striatum and cortex) reflect modulation of striatal dopamine, we compared the effects of methylphenidate with the effects of the selective D2-receptor antagonist sulpiride, which acts primarily on the striatum where D2-receptors are disproportionately abundant [27–29].

The two experiments in this large overarching pharmacological PET study were set up to test two complementary hypotheses about dopamine's role in cognitive effort. The first experiment was inspired by neurocomputational modeling work of striatal

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dopamine (Opponent actor learning: OpAL model [30]), according to which striatal dopamine increases the weight on the benefit versus cost of options by shifting the balance of activity toward the direct Go pathway away from the indirect NoGo pathway of the basal ganglia. To test this hypothesis, half of the participants included in our study completed an experiment that we recently reported in Westbrook et al. [31], where participants chose between high-effort and low-effort options, while we tracked their eye gaze. In line with the OpAL model [30], this experiment demonstrated that both methylphenidate and sulpiride boosted the selection of a high- versus low-effort task by increasing the weight on the benefits (monetary payoff) of the high-effort task. This drug effect was present only in participants with lower striatal dopamine synthesis capacity, in line with the hypothesis that dopaminergic drug effects depend on variability in striatal dopamine [2, 22, 32].

The other half of the participants included in the large pharmacological PET study completed the experiment reported here. This experiment was motivated by a different hypothesis, derived from the recent opportunity cost theory of cognitive effort [33, 34], stating that performance of cognitive control tasks is costly, because it requires task focus and persistent task engagement, which interferes with performing potentially rewarding alternative tasks. Inspired by the proposal that the opportunity cost of physical effort, equal to the average reward rate of the environment, corresponds to levels of tonic dopamine [35, 36], the opportunity cost of cognitive effort was argued to also be carried by tonic dopamine [19, 33] (but see [37, 38]). To test this hypothesis, the current paradigm maximizes sensitivity to the opportunity cost of task engagement by allowing participants to choose between task engagement and leisure (allowing pursuit of unstructured/unspecified opportunities). By contrast, our previous experiment reported in Westbrook et al. [31] required choices between high- and low-effort options, thus controlling for opportunity cost.

For the present experiment, we considered two alternative hypotheses. First, we reasoned that prolonging the action of dopamine in the synapse via methylphenidate might potentiate task disengagement, by amplifying a putatively dopamine-mediated signal of the opportunity costs of cognitive task engagement [19]. By contrast, we also considered the hypothesis that, in line with the OpAL model, methylphenidate might potentiate task engagement by shifting the balance more toward the benefits and away from the costs of cognitive work [30]. Given prior evidence for large individual variability in dopaminergic drug effects, we anticipated that this effect would depend on striatal dopamine synthesis capacity. Although sulpiride can block postsynaptic D2-receptors at higher doses [39], we predicted that the direction of sulpiride effects at the dose used in the current study (400 mg) would parallel that of methylphenidate's effects due to presynaptic autoreceptor binding, resulting in enhanced dopamine release [40, 41]. These predictions were preregistered on https://osf.io/g2z6p/.

MATERIALS AND METHODS

Data and code are available via https://osf.io/4zwu7/.

Participants

Fifty right-handed, neurologically and psychiatrically healthy volunteers were recruited as part of a larger study (detailed study overview in Supplementary Information). Participants provided written informed consent and were paid €309 upon completion of the study. The study was approved by the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands: protocol NL57538.091.16; trial register NTR6140, https://www.trialregister.nl/trial/5959). One participant dropped out during the second day due to nausea, another after four study days due to anxiety, and PET data of two other participants were incomplete (one due to scanner software problems and another due to discomfort during scanning). We analyzed data of the resulting 46 participants (age: mean(SD) = 23.8 (5.9) years; 23 women; body weight: mean(SD) = 71.0(10.1) kg).

General study overview and pharmacological manipulation

A within-subjects, cross-over and double-blind design was used, comprising five sessions. The first day served as an intake session. On the following three pharmacological sessions, participants first completed a working memory delayed response task (24 min). To ensure blinding with regard to drug condition, they then received one capsule at each of two different time points: either placebo or 400 mg sulpiride at timepoint, 1 and either placebo or 20 mg methylphenidate at timepoint 2. Participants completed a cognitive effort-discounting choice procedure (duration: 22 min) 140 min after sulpiride (or the first placebo) administration, and 50 min after methylphenidate (or the second placebo) administration. Sulpiride plasma concentrations have been found to peak after ~3 h (mean ≈ 2.9 h; SD ≈ 1.3 h [42, 43]) and methylphenidate plasma concentrations have been found to peak after ~2 h (mean ≈ 2.2 h; SD ≈ 0.8 h [44–46]). Drug timings were optimized for peak effects during an fMRI paradigm not reported here; near-peak effects were expected during the choice procedure. On the fifth day, participants underwent an [^{18}F]DOPA PET scan to quantify their dopamine synthesis capacity. See Supplementary Information for complete task battery and timings.

Behavioral paradigm

Color wheel working memory task. The color wheel task (Fig. 1a) is a delayed response working memory task assessing two distinct component processes of cognitive control: distractor resistance and flexible updating [47, 48]. A more detailed description of the paradigm and a discussion on flexibility versus stability are reported in the Supplementary Information. The primary research question of this study concerned drug effects on motivation, irrespective of the type of cognitive control process. On each trial, participants had 0.5 s to memorize the colors and locations of one to four squares (set size 1–4), followed by a 2 s fixation cross. Then, a new set of colors appeared on screen for 0.5 s, accompanied by either the letter "I" (for "ignore") or the letter "U" (for "update"). In the ignore task type, participants had to ignore the new colors and keep the previous set in memory. In the update task type, they had to update their memory with the new set of colors. This was again followed by a fixation cross, which, depending on the task type, lasted either 2 or 4.5 s, ensuring equal delay times between the relevant stimuli (first set for the ignore type and second set for the update type) and the subsequent probe. During this probe phase, participants had 4 s to indicate the color of the target square by clicking on the corresponding color on a color wheel. Participants completed 128 trials divided over two blocks, with an equal division across set sizes and task types.

Choice task. To quantify participants' cognitive motivation, participants completed a choice task (Fig. 1b), where they successively chose between repeating the color wheel task (redo option) for more money or a no-redo (rest) option for less money, in which participants would be free to do what they wanted for an equal length of time, while staying in the testing room. Participants were informed that one of their redo versus no-redo choices would be selected randomly for them to complete. Due to time constraints, and known to the participant, the entire task (i.e., both the monetary bonus and the redo of the color wheel task) was hypothetical. A strong effect of set size on proportion of redo choices validated the task manipulation, evidencing strong monotonic cognitive load-based discounting (see "Results" section). The hypothetical compensation for the redo option was fixed at €2.00. We assumed that participants

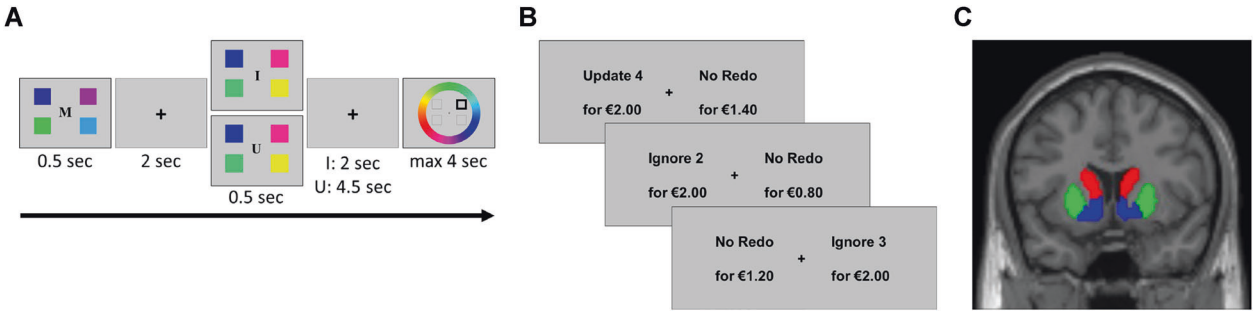

Fig. 1 Schematic of data acquisition. a Schematic of the color wheel working memory task. I = "ignore": participants have to ignore the new squares, while still remembering the previous set of squares. U = "update": participants have to remember the new set of squares and forget the previous set. **b** Example trial sequence of the cognitive effort discounting choice task. **c** Coronal view of our regions of interest, including the nucleus accumbens (blue), putamen (green), and caudate nucleus (red).

would prefer the no-redo over the redo option. However, to also accommodate the possibility of effort seeking, that is, that some participants would unexpectedly prefer the redo option over the no-redo option, we varied the compensation for the no-redo option from €0.10 to €2.20. The redo option was further specified by task type and set size, so that participants were instructed that the majority of trials in the redo block would consist of trials of the chosen task type and set size. The remainder of the trials would be randomly divided among all task-type and set-size combinations. To account for the stochastic nature of decision-making [49], we opted not to use a titration procedure for arriving at the subjective value [50], since titration adjusts the offer for the no-redo option based on previous, noisy choices. Instead, we randomly sampled choices across the full value range in three blocks of 96 trials each, equally divided across set size, task type, and monetary offer for the no-redo option.

PET acquisition and preprocessing

PET scans were acquired on a Siemens PET/CT scanner at the Department of Nuclear Medicine of the Radboudumc, using an [^{18}F]DOPA radiotracer, produced by the Radboud Translational Medicine department. Participants received 150 mg carbidopa and 400 mg entacapone 50 min before scanning, to minimize peripheral metabolism of [^{18}F]DOPA by decarboxylase and COMT, respectively, thereby increasing signal to noise ratio in the brain. After a bolus injection of [^{18}F]DOPA (185MBq; ~5 mCi) into the antecubital vein, the procedure started with a low dose CT scan (~0.75 mCi) for attenuation correction of the PET images after which a dynamic PET scan was collected over 89 min, divided into 24 frames (4 × 1, 3 × 2, 3 × 3, 14 × 5 min). PET data (4 × 4 × 3 mm voxel size; 5 mm slice thickness; 200 × 200 × 75 matrix) were reconstructed with weighted attenuation correction and time-of-flight recovery, scatter-corrected, and smoothed with a 3 mm full-width at half-maximum kernel. For registration purposes, we acquired a T1-weighted anatomical MRI scan on the first testing day, using an MP-RAGE sequence (repetition time = 2300 ms, echo time = 3.03 ms, 192 sagittal slices, field of view = 256 mm, voxel size 1 mm isometric) on a Siemens 3 T MRI scanner with a 64-channel coil. After reconstruction, PET data were preprocessed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). All frames were realigned for motion correction and coregistered to the anatomical MRI scan, using the mean PET image of the first 11 frames (using the mean image of only the first 11 frames improves coregistration, because these images have a greater range in image contrast in regions outside the striatum). Dopamine synthesis capacity was computed per voxel as [^{18}F]DOPA influx constant per minute (K_i) relative to the cerebellar gray matter reference region using Gjedde–Patlak graphical analysis on the PET frames from the 24th to 89th minute [51]. We then extracted average K_i values from three regions of interest (ROIs)—nucleus accumbens, putamen, and caudate nucleus—defined using masks based on an independent functional connectivity analysis of the striatum [52] and exactly the same as reported in Westbrook et al. [31] (Fig. 1c).

Data analysis

Performance measures on the color wheel task included median absolute degrees of deviance of the response from the correct color (deviance) and median response time (RT) for each participant. Participants' preferences on the choice task were calculated as the proportion of trials on which participants chose the redo option over the no-redo option (proportion redo). Outliers were a priori defined as those who deviated more than three standard deviations from the global mean, which did not result in any exclusions. Repeated measures ANOVAs were performed using the aov_car function from the afex package [53] in R (version 3.6.0), including drug (placebo, methylphenidate, or sulpiride), task type (ignore or update), and set size (ranging from 1 to 4) as within-subjects variables and dopamine synthesis capacity (K_i; measured as the average [^{18}F]DOPA uptake across all voxels within each ROI, mean-centered across participants) as covariate. Unless stated otherwise, we conducted an initial omnibus test, including all three drug conditions (drug(3) × task type(2) × set size(4) × K_i), followed up by three planned comparisons between each pair of drug conditions (drug(2) × task type (2) × set size(4) × K_i) and the simple three-way interaction under placebo (task type(2) × set size(4) × K_i). Separate analyses were run for each ROI—nucleus accumbens, putamen, and caudate nucleus. Greenhouse–Geisser corrections were applied when the sphericity assumption was violated. A p-value < 0.017 (Bonferroni corrected for the three ROIs) was considered significant. Partial eta squared (η_p^2) and confidence intervals were calculated using the eta.partial.SS function from the MOTE package [54] in R.

RESULTS

Working memory performance

Before drug intake, participants performed the working memory task. Across sessions and in line with earlier work [48], participants performed poorer when working memory load increased, as indicated by higher deviance ($\eta_p^2 = 0.46$, 90% CI [0.34, 0.55], $p <$ 0.001) and longer RTs ($\eta_p^2 = 0.77$, 90% CI [0.69, 0.81], $p < 0.001$). While participants deviated from the target color less on update trials ($\eta_p^2 = 0.50$, 90% CI [0.31, 0.66], $p < 0.001$), their RTs were longer compared with ignore trials ($\eta_p^2 = 0.43$, 90% CI [0.23, 0.59], $p < 0.001$). Both deviance and RT show a significant interaction (deviance: $\eta_p^2 = 0.25$, 90% CI [0.14, 0.35], $p < 0.001$; RT: $\eta_p^2 = 0.09$, 90% CI [0.02, 0.16], $p = 0.006$; Fig. 2a, b).

There was no main effect of dopamine synthesis capacity on either deviance (caudate nucleus: $\eta_p^2 = 0.01$, 90% CI [0.00, 0.12], $p = 0.471$; putamen: $\eta_p^2 = 0.00$, 90% CI [0.00, 0.06], $p = 0.795$; nucleus accumbens: $\eta_p^2 = 0.01$, 90% CI [0.00, 0.09], $p = 0.634$) or RT

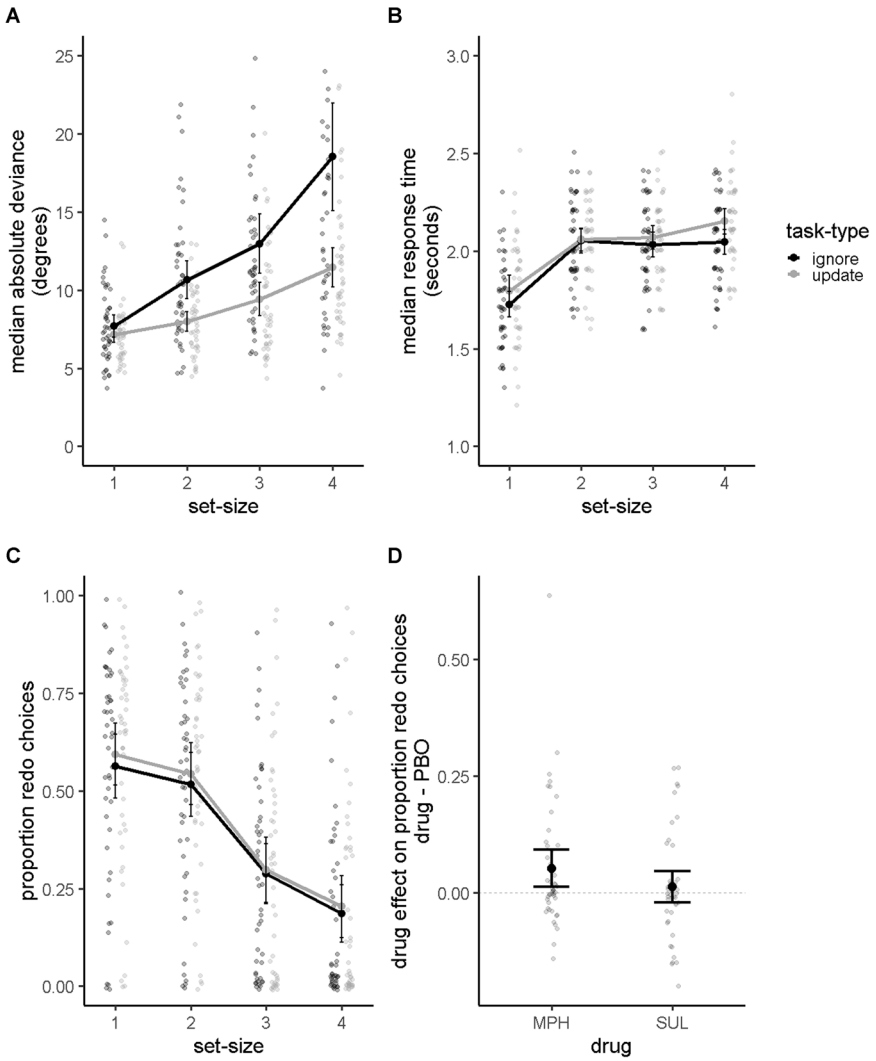

Fig. 2 Behavioral results. a Median absolute deviance, **b** median response times, and **c** the proportion of trials on which participants chose the redo option across drug sessions plotted as a function of set size, separately for each task type. **d** Drug effect on the proportion of trials on which participants chose the redo option (methylphenidate or sulpiride minus placebo). The methylphenidate-induced effect on proportion redo choices is still significant without the participant showing the greatest effect: $F_{(2,86)} = 4.0$, $p = 0.022$. Error bars represent 95% confidence interval around the mean. MPH methylphenidate, SUL sulpiride, PBO placebo.

(caudate nucleus: $\eta_p^2 = 0.00$, 90% CI [0.00, 0.05], $p = 0.842$; putamen: $\eta_p^2 = 0.01$, 90% CI [0.00, 0.10], $p = 0.577$; nucleus accumbens: $\eta_p^2 = 0.00$, 90% CI [0.00, 0.09], $p = 0.661$), nor did dopamine synthesis capacity interact with any of the other variables.

Methylphenidate increased cognitive motivation

Under placebo, participants exhibited a preference for not repeating any task, as evidenced by the proportion redo being significantly <0.5 (proportion = 0.38, SD = 0.24; Cohen's $d = -0.51$, 95% CI (−0.82, −0.20), $p = 0.001$). As hypothesized, we found a significant effect of drug on proportion redo (main effect of drug with three conditions: $\eta_p^2 = 0.10$, 90% CI [0.02, 0.21], $p = 0.008$). This was driven by higher proportion redo under methylphenidate versus placebo ($\eta_p^2 = 0.15$, 90% CI [0.03, 0.33], $p = 0.007$; Fig. 2d). There was no difference between sulpiride and placebo ($\eta_p^2 = 0.01$, 90% CI [0.00, 0.12], $p = 0.443$; Fig. 2d). Numerically, proportion redo was higher under methylphenidate than sulpiride, but this difference did not survive correction for multiple comparisons ($\eta_p^2 = 0.12$, 90% CI [0.01, 0.29], $p = 0.021$). Proportion redo decreased with set size ($\eta_p^2 = 0.64$, 90% CI [0.55, 0.71], $p < 0.001$; Fig. 2c). There was no effect of task type ($\eta_p^2 = 0.03$, 90% CI [0.00, 0.15], $p = 0.268$), and no interaction between task type and set size ($\eta_p^2 = 0.03$, 90% CI [0.00, 0.08], $p = 0.247$), nor did drug interact with task type ($\eta_p^2 = 0.02$, 90% CI [0.00, 0.03], $p = 0.478$) or set size ($\eta_p^2 = 0.02$, 90% CI [0.00, 0.07], $p = 0.496$).

High-dopamine participants exhibited greater methylphenidate-related increases in cognitive motivation

The effect of methylphenidate on proportion redo depended on dopamine synthesis capacity. This was supported by a significant interaction between drug (methylphenidate, sulpiride, and placebo) and dopamine synthesis capacity in the nucleus accumbens ($p = 0.009$; Fig. 3b, c and Table 1). Participants with higher dopamine synthesis capacity in the nucleus accumbens exhibited greater methylphenidate-induced increases in proportion redo choices than participants with lower dopamine synthesis capacity ($p = 0.006$). The drug by dopamine synthesis capacity interaction for sulpiride versus placebo ($p = 0.314$) and for methylphenidate versus sulpiride ($p = 0.034$) were not significant, after correction for multiple comparisons. Although subthreshold, interactions in the same direction were found between drug and dopamine synthesis capacity in the putamen and caudate nucleus (Fig. 3b, c and Table 1). A negative association between dopamine synthesis

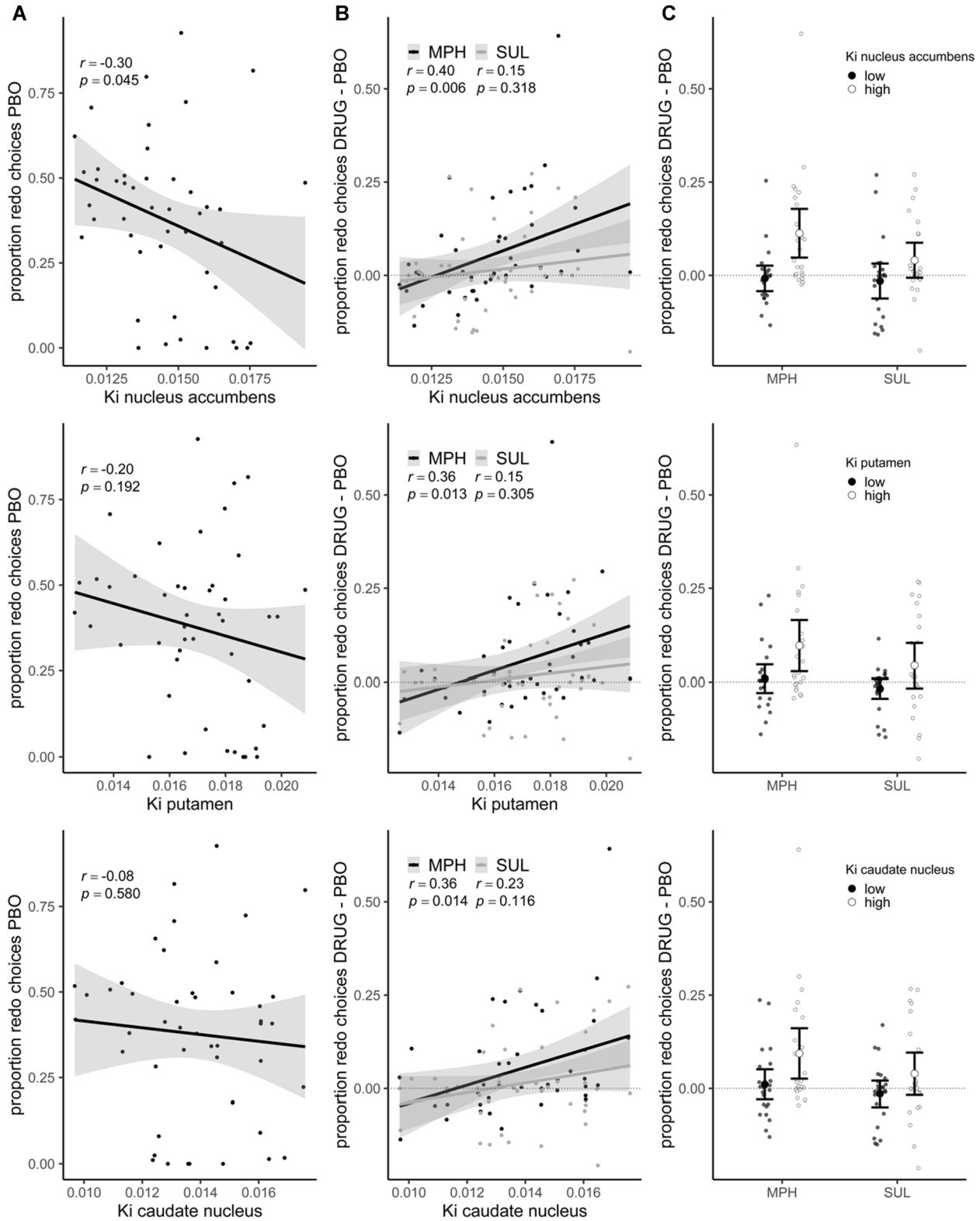

Fig. 3 Proportion redo choices as a function of dopamine synthesis capacity in the nucleus accumbens (upper panels), putamen (middle panels), and caudate nucleus (bottom panels). *P*-values < 0.017 were considered significant. **a** Correlation between dopamine synthesis capacity and proportion redo choices under placebo. **b** Correlation between dopamine synthesis capacity and drug-induced changes in proportion redo choices. Correlation coefficients and *p*-values without the participant showing the greatest methylphenidate-induced effect on proportion redo choices: $r_{\text{nucleus accumbens}} = 0.36$, $p = 0.014$; $r_{\text{putamen}} = 0.41$, $p = 0.005$; $r_{\text{caudate nucleus}} = 0.29$, $p = 0.056$. **c** Median split on dopamine synthesis capacity for visualization purposes. Shaded areas and error bars represent 95% confidence interval around the mean. PBO placebo, MPH methylphenidate, SUL sulpiride, K_i [^{18}F]DOPA uptake.

capacity and proportion redo choices under placebo was not significant (Fig. 3a and Table 1). Importantly, supplementary analyses demonstrated that the effect of methylphenidate on proportion redo does not reflect changes in choice randomness, effects on task performance (completed prior to drug administration), or effects on mood and medical symptoms. The effect is reproduced when analyzing "indifference points" and when controlling for (a failure to counterbalance) session order (Supplementary Information).

Drug manipulation does not interact with the benefit of engaging in a cognitive task

Primary analyses on proportion redo choices revealed no significant interactions between drug and the cognitive cost of the task—the set size. We also explored whether drug effects interacted with the benefit of the task—the monetary payoff for the redo option relative to the no-redo option. Note that the payoff of the redo options was constant throughout the task. To that end, we added, in an additional analysis, the monetary payoff for the no-redo option to our rmANOVA. Because each monetary value was only repeated three times per drug session, task type, and set size, we divided these values into tertiles so that proportion redo was calculated based on 12 trials. As expected, the monetary payoff had a strong negative main effect on proportion redo ($\eta_p^2 = 0.72$, 90% CI [0.62, 0.79], $p < 0.001$), such that the higher the payoff for the no-redo option, the less often people chose the redo option. Although numerically there was a greater methylphenidate-related increase in proportion redo when the payoff for the no-redo option was lower (i.e., when the benefit for the task was higher), payoff did not significantly interact with drug ($\eta_p^2 = 0.05$, 90% CI [0.00, 0.10], $p = 0.062$) or with the interaction of drug with dopamine synthesis capacity (nucleus accumbens: $\eta_p^2 = 0.02$, 90% CI [0.00, 0.04], $p = 0.562$; putamen: $\eta_p^2 = 0.02$, 90% CI [0.00, 0.04], $p = 0.513$; caudate nucleus: $\eta_p^2 = 0.02$, 90% CI [0.00, 0.04], $p = 0.456$). Thus, while the possibility of unstructured free time comprised unmeasured opportunity costs of engaging in the task, drug manipulation did not reliably affect the sensitivity to the relative, explicit costs, or benefits of the redo option.

High-dopamine participants exhibited greater methylphenidate-related slowing of choice latency

Exploratory analyses of choice latency revealed no main effect of drug ($\eta_p^2 = 0.01$, 90% CI [0.00, 0.03], $p = 0.794$). There was a significant interaction between effect of drug on choice latency and dopamine synthesis capacity in the nucleus accumbens ($p = 0.005$) and putamen ($p = 0.002$; Table 1), which was driven by a difference between methylphenidate and placebo (nucleus accumbens: $p = 0.002$; putamen: $p < 0.001$; Table 1 and Fig. 4b, c). Methylphenidate slowed people with higher dopamine synthesis capacity and invigorated people with lower dopamine synthesis capacity. No significant interactions between dopamine synthesis capacity and the effect of sulpiride ($p > 0.096$), or between dopamine synthesis capacity and the difference between methylphenidate and sulpiride ($p > 0.021$) were observed (Table 1). A significant negative association between dopamine synthesis capacity and choice latency under placebo was present in the nucleus accumbens ($p < 0.001$) and putamen ($p = 0.010$), but not in the caudate nucleus ($p = 0.063$), indicating that higher dopamine synthesis capacity was associated with faster responding (Fig. 4a and Table 1).

Positive correlation between drug-induced effects on cognitive motivation and choice latency

Individuals who showed greater methylphenidate-related increases in proportion redo also showed greater methylphenidate-related slowing (Pearson's $r = 0.67$, 95% CI [0.48, 0.81], $p < 0.001$). A similar positive correlation was present between the effect of sulpiride versus placebo on choice latency and the drug effect on proportion redo ($r = 0.50$, 95% CI [0.24, 0.69], $p < 0.001$).

All region-of-interest based results were corroborated by voxel-wise K_i analyses (Supplementary Information), of which the unthresholded statistical maps are available in the NeuroVault.org database at https://neurovault.org/collections/8306/.

DISCUSSION

The present study demonstrates that methylphenidate boosts motivation for cognitive task performance over leisure. This effect was present across the group as a whole, but was particularly strong in people with high ventral striatal dopamine synthesis capacity. This finding is consistent with the OpAL model [30], stating that methylphenidate reduces the weight on the cost of task engagement. Together with the findings reported in Westbrook et al. [31], these data strengthen the link between striatal dopamine and cognitive motivation [18, 55], and the hypothesis that the cognitive enhancing effect of methylphenidate reflects an increase in motivation. The present study design provides a particularly good test of drug-induced changes in participants' cognitive motivation, rather than capacity, because methylphenidate was administered after the task-performance phase, but before the discounting phase. Moreover, the data firmly establish the pervasive baseline-dependency hypothesis of individual variability in the efficacy of the most commonly used catecholaminergic drug, methylphenidate.

The present paradigm was more sensitive to the motivational boosting effect of methylphenidate, which was observed across the group as a whole, than the paradigm in Westbrook et al. [31], where the effect was detected only in low-dopamine participants. This likely reflects the greater sensitivity of the current paradigm, at baseline, to task avoidance, as evidenced by a strong preference for the rest option. We argue that this increased sensitivity to task avoidance of the present paradigm reflects the increased opportunity cost of task engagement: by choosing the task option, they also chose to forego an opportunity to rest and play with their smartphone and/or laptop. This sensitivity to the opportunity cost at baseline, which tended to be greater in high-dopamine participants, might have rendered greater dynamic range for methylphenidate-related decreases in the weight on the cost. Conversely, Westbrook et al. required choices between a high-effort option for more money and a low-effort option for less money. This setup controlled for opportunity costs, and generated a default preference for the high-reward high-effort task. This higher preference for the effortful option at baseline, particularly in high-dopamine participants, might have reduced the range for further increases in the weight on the benefits in those participants. In short, the two paradigms likely differ in their sensitivity to increases in the benefits versus decreases in the costs by methylphenidate. This is supported by the finding that the effect of methylphenidate in the previous experiment, but not the current experiment, interacted with monetary payoff. Critically, the differential sensitivity of the two paradigms to changes in the benefits versus (opportunity and/or effort) costs of cognitive effort might also underlie the observation that methylphenidate effects are greater in high-dopamine participants in the present experiment but, conversely, in low-dopamine participants in Westbrook et al. Future studies might address the question whether the different types of effort costs and benefits implicate dopamine in distinct subregions of the striatum. This hypothesis is raised cautiously by the finding that the effect of methylphenidate on effort selection in the present study depends most strongly on dopamine synthesis capacity in the nucleus accumbens, whereas the effect in Westbrook et al. depends most strongly on dopamine in the caudate nucleus.

According to the OpAL model [30], methylphenidate might have reduced the cost of cognitive effort in this study by

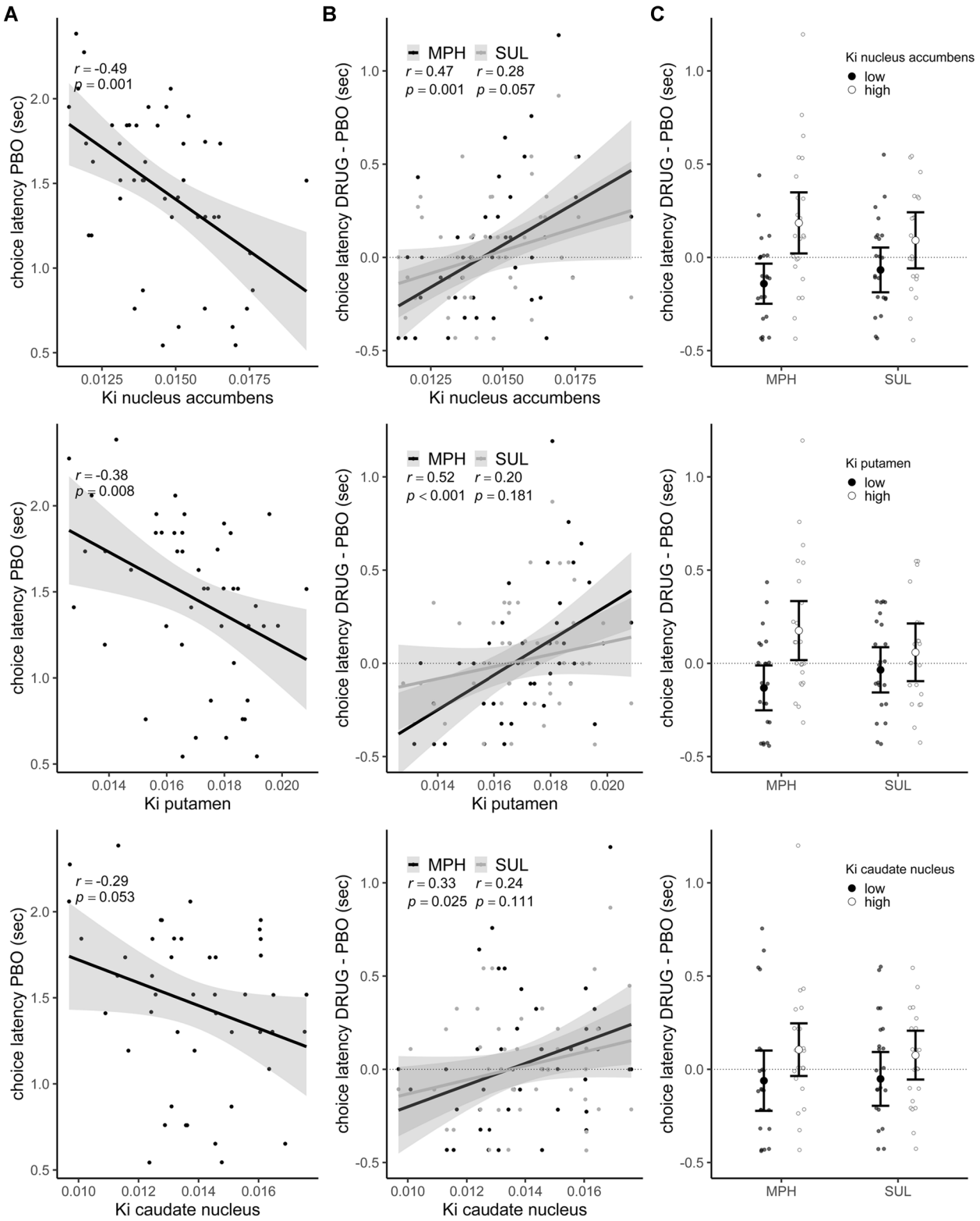

Fig. 4 Choice latency as a function of dopamine synthesis capacity in the nucleus accumbens (upper panels), putamen (middle panels), and caudate nucleus (bottom panels). *p*-Values < 0.017 were considered significant. **a** Correlation between dopamine synthesis capacity and choice latency under placebo. **b** Correlation between dopamine synthesis capacity and drug-induced changes in choice latency. **c** Median split on dopamine synthesis capacity for visualization purposes. Shaded areas and error bars represent 95% confidence interval around the mean. PBO placebo, MPH methylphenidate, SUL sulpiride, K_i [^{18}F]DOPA uptake.

Table 1. Repeated measures ANOVAs on proportion redo choices and choice latency.

	Nucleus accumbens		Putamen		Caudate nucleus	
Proportion redo choices						
	η_p^2	*p*	η_p^2	*p*	η_p^2	*p*
MPH, SUL, PBO	0.10 [0.02, 0.20]	0.009	0.08 [0.01, 0.18]	0.021	0.08 [0.01, 0.18]	0.025
Post hoc						
MPH, PBO	0.16 [0.03, 0.34]	0.006	0.13 [0.02, 0.31]	0.012	0.13 [0.02, 0.31]	0.013
SUL, PBO	0.02 [0.00, 0.14]	0.314	0.02 [0.00, 0.15]	0.298	0.06 [0.00, 0.20]	0.114
MPH, SUL	0.10 [0.00. 0.26]	0.034	0.07 [0.00, 0.23]	0.068	0.04 [0.00, 0.17]	0.204
PBO	0.09 [0.00, 0.25]	0.044	0.04 [0.00, 0.17]	0.189	0.01 [0.00, 0.10]	0.574
Choice latency						
MPH, SUL, PBO	0.11 [0.02, 0.22]	0.005	0.13 [0.03, 0.24]	0.002	0.05 [0.00, 0.13]	0.113
Post hoc						
MPH, PBO	0.20 [0.05, 0.38]	0.002	0.22 [0.06, 0.41]	<0.001	0.08 [0.00, 0.24]	0.056
SUL, PBO	0.06 [0.00, 0.21]	0.096	0.03 [0.00, 0.16]	0.254	0.06 [0.00, 0.20]	0.115
MPH, SUL	0.06 [0.00, 0.21]	0.103	0.12 [0.01, 0.29]	0.021	0.01 [0.00, 0.10]	0.569
PBO	0.22 [0.07, 0.41]	<0.001	0.14 [0.02, 0.32]	0.010	0.08 [0.00, 0.23]	0.063

Separate analysis for each ROI—nucleus accumbens, putamen, and caudate nucleus, including drug, set size, and task type, as within-subjects variables and dopamine synthesis capacity (measured as the mean-centered average [^{18}F]DOPA uptake, K_i) as covariate. Partial eta squared (η_p^2), 90% confidence intervals around η_p^2, and *p*-values for the interaction between dopamine synthesis and drug are shown, as well as the main effect of dopamine synthesis capacity on the placebo session.
MPH methylphenidate, *SUL* sulpiride, *PBO* placebo.
p-Values below a Bonferroni-corrected alpha-value of 0.017 were considered significant.

decreasing activity in the NoGo pathway of the basal ganglia. An alternative account of the observed effect is motivated by the "inverted-U" hypothesis of dopamine, which states that dopaminergic drugs shift dopamine levels from suboptimal to optimal levels in low-dopamine individuals, while shifting them from optimal to supraoptimal levels in high-dopamine individuals [2]. Specifically, methylphenidate might have decreased task motivation in low-dopamine subjects by increasing the (intrinsic) value of the rest option, while increasing task motivation in high-dopamine subjects by detrimentally "overdosing" the (intrinsic) value of the rest option.

Exploratory analyses revealed a strong negative association between choice latency and dopamine synthesis capacity under placebo. While methylphenidate sped up choices of participants with low-dopamine synthesis capacity, it slowed choices of participants with higher dopamine synthesis capacity. Intriguingly, these striatal dopamine-dependent effects of methylphenidate on choice latency correlated with the effects of methylphenidate on cognitive effort choice. One explanation of this effect is that the strength of the default preference for no-redo was strongest for people with high-dopamine synthesis capacity. Because these participants showed the largest shift away from a default preference on methylphenidate, they might have experienced greater choice conflict, accounting for their slowing.

The clinical implications of the current results for populations who commonly get prescribed methylphenidate have yet to be determined. Studies of the relationship between impulse control disorders and striatal dopamine synthesis capacity have produced contrasting results, with enhanced capacity in pathological gamblers [56], conflicting results in substance abusers [57–60], and if anything reduced capacity in ADHD patients [61, 62].

A limitation of the current pharmacological PET study is that it does not allow us to directly address the neural locus of methylphenidate's effect. The finding that the effects of methylphenidate were associated with striatal dopamine synthesis capacity suggests that methylphenidate acted on the striatum to modulate cognitive motivation. However, given that [^{18}F]DOPA uptake signal is too low in the prefrontal cortex, we cannot exclude the possibility that the variation in nigrostriatal dopamine synthesis capacity is paralleled by variation in prefrontal dopamine levels. An additional prefrontal locus of effect is also consistent with the absence of significant effects of sulpiride, which acts selectively on dopamine D2-receptors that are particularly abundant in the striatum. In future studies, pharmacology and PET should be combined with functional magnetic resonance imaging to isolate the neural locus of the dopamine-dependent effects of methylphenidate on cognitive motivation.

The finding that the effects of methylphenidate, which blocks both dopamine and noradrenaline transporters [63, 64], were not accompanied by significant effects of the selective D2-receptor antagonist sulpiride is surprising. First, previous research has established that the present dose of sulpiride is effective at ~2 h after intake, indexed in terms of both sulpiride plasma concentrations [42, 43] and behavioral effects on reversal learning [65]. Second, the exact same dose of sulpiride did have a significant effect in Westbrook et al. [31], where the exact same study protocol was applied. This might lead some to ask whether the current effects reflect a modulation of noradrenaline instead of dopamine [66–70]. However, given the lack of sulpiride-related changes in physiological or subjective report measures (Supplementary Information), we cannot exclude the possibility that the drug manipulation did not alter behavior on the current task due to for example, suboptimal timing or dosing. It is known that sulpiride can bind to both presynaptic and postsynaptic D2-receptors, with low doses (50–150 mg) primarily binding presynaptically and high doses (>800 mg) primarily binding postsynaptically [40, 71, 72]. The 400 mg used in the current study might thus have had mixed presynaptic and postsynaptic effects, canceling each other out. Nevertheless, the pattern of sulpiride effects resembled that of methylphenidate, with the difference between the two drugs not reaching significance. It is uncertain whether this represents a true difference between the effects of sulpiride and methylphenidate, a suboptimal dose that had a presynaptic effect in most participants, but was sufficiently high to have a primarily postsynaptic effect in some participants, or rather a lack of statistical power to detect sulpiride-induced effects. Given that methylphenidate's effects were predicted by [^{18}F]DOPA

uptake in the striatum (which does not contain any noradrenaline receptors), and the resemblance between the pattern of effects of methylphenidate and sulpiride, we argue that they likely reflect modulation of dopamine rather than noradrenaline. Indeed this conclusion also concurs with prior evidence that methylphenidate's enhancing effects correspond with changes in midbrain dopamine release [73].

In conclusion, this study suggests that methylphenidate reduces the cost of mental labor by increasing striatal dopamine, thus strengthening the motivational account of methylphenidate's effects on cognition.

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AUTHOR CONTRIBUTIONS

Conceptualization: RC; methodology: RC, DP, MIF, BBZ, and LH; software: DP, LH, and RvdB; formal analysis: LH, RvdB, and RC; investigation: LH, DP, RvdB, JIM, and R-JV; data curation: LH, DP, RvdB, and JIM; writing—original draft preparation: LH and RC, writing—review and editing: LH, DP, RvdB, JIM, MIF, BBZ, AW, R-JV, and RC; and visualization: LH and BBZ supervision: RC; project administration: JIM; and funding acquisition: RC.

ADDITIONAL INFORMATION

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