TITLE

Baseline dopamine predicts individual variation in methylphenidate's effects on cognitive motivation

AUTHORS

Lieke Hofmans, M.S.[1,2], Danae Papadopetraki, M.S.[1,2], Ruben van den Bosch, M.S.[1,2], Jessica I. Määttä, M.S.[1,2], Monja I. Froböse, Ph.D.[1], Bram. B. Zandbelt, Ph.D.[1,2], Andrew Westbrook, Ph.D.[1,2,3], Robbert-Jan Verkes, M.D., Ph.D.[2,4,5], Roshan Cools, Ph.D.[1,2]

AFFILIATIONS

[1]Donders Institute for Brain, Cognition & Behaviour, Radboud University, Nijmegen, The Netherlands

[2]Department of Psychiatry, Radboudumc, Nijmegen, The Netherlands

[3]Department of Cognitive Linguistics and Psychological Sciences, Brown University, Providence, The United States of America

[4]Forensic Psychiatric Centre Nijmegen, Pompestichting, Nijmegen, The Netherlands.

[5]Department of Criminal Law, Law School, Radboud Universiteit, Nijmegen, The Netherlands

CORRESPONDING AUTHOR

Lieke Hofmans, Kapittelweg 29 r.2.269, 6525EN Nijmegen, The Netherlands

tel.: +310243614305 | Fax: +310243610989

e-mail: l.hofmans@donders.ru.nl

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ABSTRACT

Contrasting cognitive effects of dopaminergic drugs, for example in low- and high-impulsive individuals, have long been argued to reflect variability in baseline levels of dopamine. Here, we investigated whether individual differences in the effects of methylphenidate on cognitive motivation depend on baseline dopamine synthesis capacity. Fifty healthy participants (25 women) underwent an [^{18}F]DOPA PET scan to quantify baseline dopamine synthesis capacity. They performed an effortful working memory task prior to drug administration and a cognitive effort discounting task after drug administration. To examine the neurochemical specificity to dopamine, effects of methylphenidate were compared with those of the selective dopamine D2 receptor antagonist sulpiride. Participants also completed a questionnaire to assess trait impulsivity. Methylphenidate increased cognitive motivation to a greater extent in people with high baseline midbrain dopamine synthesis capacity than in people with low baseline midbrain dopamine. Parallel effects were observed as a function of trait impulsivity, with high-impulsive participants exhibiting greater motivational enhancing effects than low-impulsive participants. This effect was fully mediated by baseline dopamine. There were no significant effects of sulpiride. This study provides a link between motivational enhancement by methylphenidate, baseline dopamine and trait impulsivity, thereby advancing the biological understanding of individual variation in the effects of methylphenidate.

Disclaimer: we have discovered a mistake in our measure of impulsivity (BIS-11). Currently, we are in the process of correcting the scores and assessing the extent to which this would change the impulsivity-related results and conclusions.

INTRODUCTION

Cognitive control refers to a set of mechanisms required for adaptively pursuing a (long term) goal, involving, among other things, the preparation and maintenance of rules to bias action and attention in working memory [1] and is well known to implicate catecholamine transmission [2–4]. Drugs altering catecholamine transmission are first-line treatment for disorders accompanied by deficits in cognitive control, such as attention deficit/ hyperactivity disorder (ADHD) [5, 6] and are commonly used for cognitive enhancement in healthy people [7–9]. Various studies have demonstrated that acute administration of psychostimulants, like the dopamine and noradrenaline transporter blocker methylphenidate, enhances cognitive control in healthy individuals [10–15].

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 [2]. However, recent progress suggests that the recruitment of cognitive control might also be altered by changing motivation, rather than ability alone [16]. In line with this hypothesis, catecholaminergic interventions in rodents and humans have been shown to affect effort-based decision making and cognitive motivation, without affecting performance [17–20] (but see [21]).

However, there is large individual variation in dopaminergic drug effects on motivation. For example, administration of amphetamine to experimental rodents increased cognitive motivation in 'slackers', while decreasing it in 'workers' [22]. Such contrasting effects on cognitive motivation are reminiscent of the variable effects of methylphenidate (and selective dopamine receptor agonists, such as bromocriptine) on task performance, with greater beneficial effects in participants with higher trait impulsivity [23, 24] or with poorer baseline performance on a sustained attention task [25]. These trait dependencies are consistent with classic psychostimulant 'rate-dependent' effects [26, 27]: having

calming effects on hyperactivity in children with (and without) ADHD [28], while, by contrast, increasing activity in fatigued or sleep-deprived adults [29].

It has long been argued that such contrasting effects of dopaminergic drugs, for example in low- and high-impulsive individuals, reflect variability in baseline levels of dopamine [3]. However, there is no direct evidence that the principle of baseline-dependency applies also to the most commonly used psychostimulant drugs like methylphenidate. Here, we test the hypothesis that the effects of methylphenidate on cognitive motivation depend on baseline dopamine synthesis capacity. Participants completed a cognitive effort discounting task after drug administration. In a separate session they underwent an [^{18}F]DOPA PET scan to quantify baseline 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, unlike other dopamine PET tracers such as [^{11}C]raclopride or [^{18}F]fallypride, which reflect D2/3 receptor availability, is less sensitive to state-dependent changes in dopamine levels [30] (but see [31]). To substantiate the hypothesis that the effects of the non-specific 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 sulpiride, which acts primarily on the striatum due to its selectivity for D2 receptors that are disproportionately abundant in the striatum [32–34]. We predicted that cognitive motivation would not only be sensitive to methylphenidate but also to sulpiride, based on a considerable body of literature demonstrating the importance of the D2 receptor in value computation, as well as evidence indicating significant effects of D2 agents on both physical and cognitive effort-based choice [21, 35–40].

MATERIALS AND METHODS

Participants

Fifty right-handed, neurologically and psychiatrically healthy volunteers (18-43 years at start of study, mean(SD) = 24(5.7); 25 women) were recruited as part of a larger study (detailed study overview in Supplementary information). This sample size enabled us to detect correlations with an effect size of at least 0.52[41]. 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 behavioral data of the resulting 49 participants and PET data of the resulting 46 participants.

General study overview and pharmacological manipulation

The study consisted of 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, then they were administered an oral dose of either 20mg of methylphenidate, or 400mg of sulpiride, or placebo. After drug administration, participants completed a cognitive effort-discounting choice procedure. On the fifth day, participants underwent an [^{18}F]DOPA PET scan to quantify their baseline dopamine synthesis capacity.

Behavioral paradigm

Color wheel working memory task

The color wheel task (Figure 1A) is a delayed response working memory task assessing two distinct component processes of cognitive control: distractor resistance and flexible updating [42, 43]. 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 the motivation for either type of cognitive control process (see https://osf.io/g2z6p/ for preregistration). On each trial, participants had 0.5s to memorize the colors and locations of one to four squares (set-size 1-4), followed by a 2s fixation cross. Then, a new set of colors appeared on screen for 0.5s, 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 2s or 4.5s, 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 4s to indicate the color of the target square by clicking on the corresponding color on a color wheel. Participants completed 128 trials divided over 2 blocks, with an equal division across set-sizes and task-types.

Choice task

To quantify participants' cognitive motivation, participants completed a choice task (Figure 1B) where they successively chose between repeating a block of the color wheel task (redo option) for more money or a no-redo 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 choices would be randomly selected. Due to time constraints, and known to the participant, both the monetary bonus and the redo of the color wheel task were 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). The hypothetical compensation for the redo option was fixed at €2.00. The compensation for the no-redo option ranged 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 probabilistic nature of decision making, we opted not to use a titration procedure for arriving at the subjective value [44], but instead randomly sampled choices across the full value-range in 3 equivalent 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 150mg of carbidopa and 400mg of entacapone 50 minutes 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; approximately 5mCi) into the antecubital vein, a dynamic PET scan was collected over 89 minutes and divided into 24 frames (4x1, 3x2, 3x3, 14x5 min). PET data (4 x 4 x 3mm voxel size; 5mm slice thickness; 200 x 200 x 75 matrix) were reconstructed with weighted attenuation correction and time-of-flight recovery, scatter corrected, and smoothed with a 3mm full-width-at-half-maximum (FWHM) kernel. For registration purposes we acquired a T1-weighted anatomical MRI scan on the first testing day on a Siemens 3T MR 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 and coregistered to the anatomical MRI scan. Dopamine synthesis capacity was

computed per voxel as [^{18}F]DOPA influx constant per minute (K_i) relative to the cerebellar grey matter reference region using Gjedde-Patlak graphical analysis on the PET frames from the 24th to 89th minute [45]. The resulting individual K_i maps were spatially normalized and smoothed using an 8mm FWHM kernel (more details can be found in the Supplemental information).

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 reaction 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. Analyses based on indifference points are reported in Supplementary information.

Data were analysed using repeated-measures ANOVA in SPSS (IBM SPSS Statistics, version 23.0, 2015) with the within-participant factors drug (placebo, methylphenidate, or sulpiride), task-type (ignore or update) and set-size (ranging from 1 to 4). Greenhouse–Geisser corrections were applied when the sphericity assumption was violated. A *p*-value smaller than 0.05 was considered significant. To allow for quantification of evidence for or against our hypotheses, we additionally report Bayesian individual effects analyses performed in JASP (version 0.10.2.0), with default JASP Cauchy priors. The $BF_{inclusion}$ reflects how well the effect predicts the data by comparing the performance of all models that include the effect to the performance of all models that do not include the effect. When frequentist and Bayesian statistics were inconsistent, we based our conclusions on Bayesian sequential analyses of the individual effects, using the BayesFactor [46] and bayestestR packages [47] in R [48].

To assess baseline dopamine-dependency, we conducted a voxel-wise correlation of K_i influx constant values with our behavioral measures. We restricted our search, following prior procedures [49], to one region of interest comprising all voxels that exhibited a K_i value of 3 standard deviations above the global mean. This region of interest included the striatum and midbrain (8993 voxels; Figure 1C-E). Statistical significance was defined as family-wise error (FWE) corrected $p<0.05$ at peak coordinate, after small volume correction for all voxels within the region of interest. Analyses controlling for session order and mood, medical symptoms and physiological measures are reported in the Supplementary information.

Trait impulsivity

In exploratory analyses, we assessed whether trait impulsivity, measured as total BIS-11 score [50], was associated with the effect of drug on proportion no-redo choices and RTs on the choice task, by performing Pearson's correlations (see Supplementary information for BIS-11 sub-scale analyses). Additionally, we conducted mediation analyses assessing whether associations between impulsivity and methylphenidate's effects were mediated by baseline dopamine synthesis capacity (see Supplementary information for details and results).

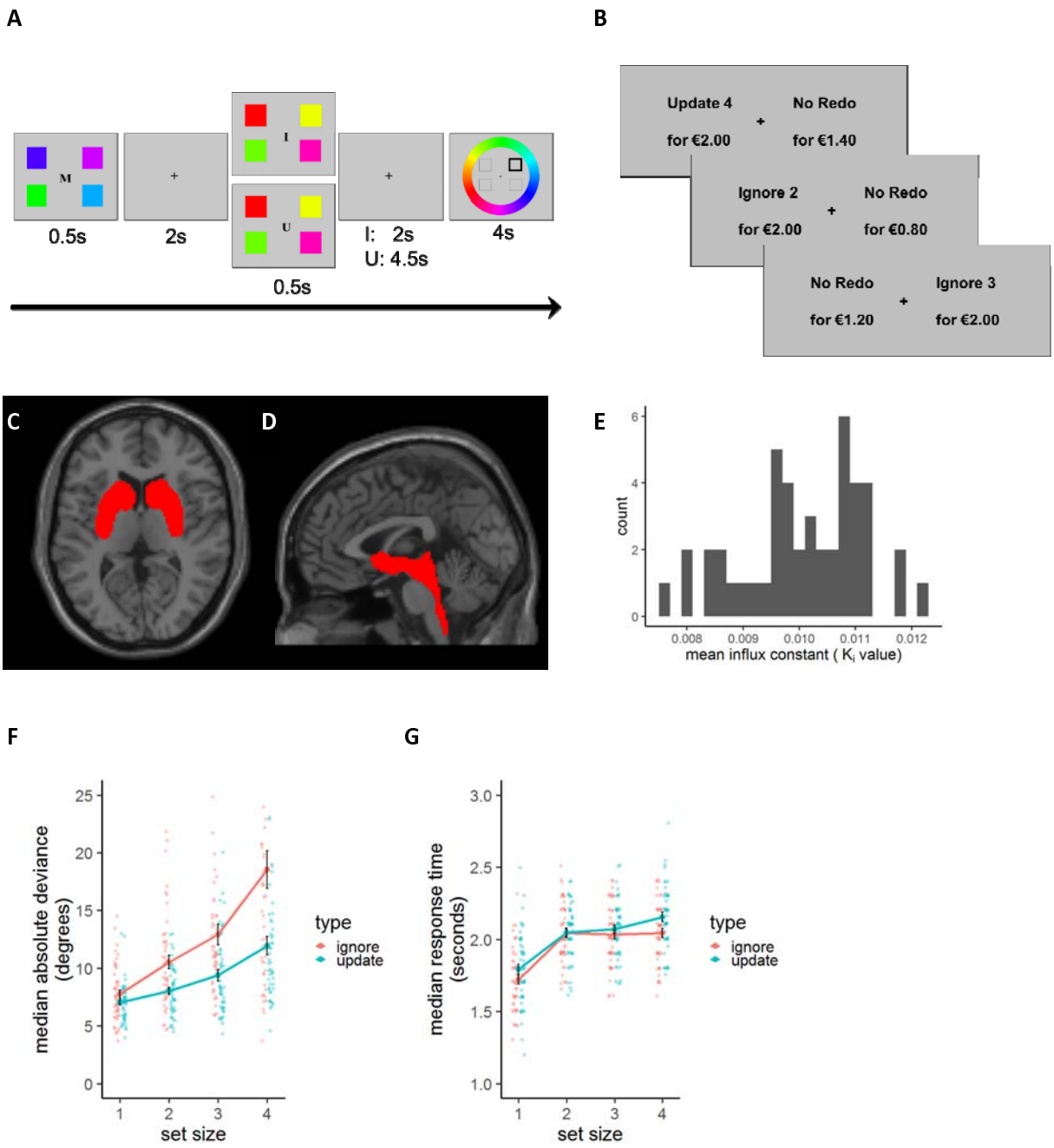

Figure 1. **A** – Schematic of the color wheel working memory task. I = 'ignore': participants have to ignore the new squares while still remembering the previous set of squares. U = 'update': participants have to remember the new set of squares and forget the previous set. **B** – Example trial sequence of the cognitive effort discounting choice task. **C** – Axial and **D** – sagittal view of the group-based small volume mask including all voxels with a K_i value of > 3 SD from the global mean. **E** – Histogram of mean K_i value within the group-based mask. Count represents number of participants. N = 46. The mean K_i values varied between 0.00768 and 0.01228. These values are comparable with previous reports [51]. **F** –

Median absolute deviance and **G** – median response times across drug sessions plotted as a function of set-size, separately for each task-type. Dots represent median scores per individual. Error bars represent standard errors of the mean. $N = 49$.

RESULTS

Working memory performance decreased with set-size

Across sessions, participants showed higher deviance scores for higher set-sizes ($F_{(1.59, 76.27)} = 39.7$, $p < 0.001$; BF_{INC} = inf) and for ignore versus update trials ($F_{(1, 48)} = 46.4$, $p < 0.001$; BF_{INC} = 1.7e+11). The difference between ignore and update was larger under higher set-sizes ($F_{(1.67, 80.07)} = 12.3$, $p < 0.001$; BF_{INC} = 7.7e+2; Figure 1F).

Median reaction times (across drug sessions) also showed that participants were slower with increasing set-size ($F_{(2.52, 120.71)} = 143.6$, $p < 0.001$; BF_{INC} = 5.0e+14) and slower on update versus ignore trials ($F_{(1, 48)} = 33.8$, $p < 0.001$; 2.4e+4). The interaction between set-size and task-type was also significant ($F_{(3, 144)} = 5.4$, $p = 0.001$; BF_{INC} = 16.3; Figure 1G).

There were no correlations between individual differences in working memory task performance (all measured off drug) and individual differences in dopamine synthesis capacity (Supplementary information).

Cognitive motivation decreased with set-size

Across all choices, participants exhibited a preference for not repeating any task, as evidenced by a low average proportion redo (proportion = 0.41, SD = 0.22). Proportion redo decreased with set-size ($F_{(1.34,}$

$_{64.47)}$ = 85.9, p < 0.001; BF_{INC} = inf; Figure 2A). There was no effect of task-type ($F_{(1, 48)}$ = 0.9, p = 0.345; BF_{INC} = 0.1) and no interaction between task-type and set-size ($F_{(2.24, 107.51)}$ = 1.8, p = 0.164; BF_{INC} = 4.0e-3).

Methylphenidate increased cognitive motivation

As hypothesized, we found a significant effect of drug on proportion redo (main effect of drug with 3 levels: $F_{(2, 96)}$ = 3.5, p = 0.034; BF_{INC} = 3.1). This was driven by an effect of methylphenidate versus placebo (main effect of drug with 2 levels: $F_{(1, 48)}$ = 5.3, p = 0.026; BF_{INC} = 12.9; Figure 2B; Figure 2B). There was no difference between sulpiride and placebo (main effect of drug with 2 levels: $F_{(1, 48)}$ = 0.8, p = 0.362; BF_{INC} = 0.1; Figure 2B). Numerically, proportion redo was higher under methylphenidate than under sulpiride, but this difference was not significant (main effect of drug with 2 levels: $F_{(1, 48)}$ = 3.4, p = 0.071; BF_{INC} = 0.7). There were no statistically significant two-way interactions between drugs and set-size or task-type (see Supplementary information for a less robust three-way interaction and analysis of choice latency).

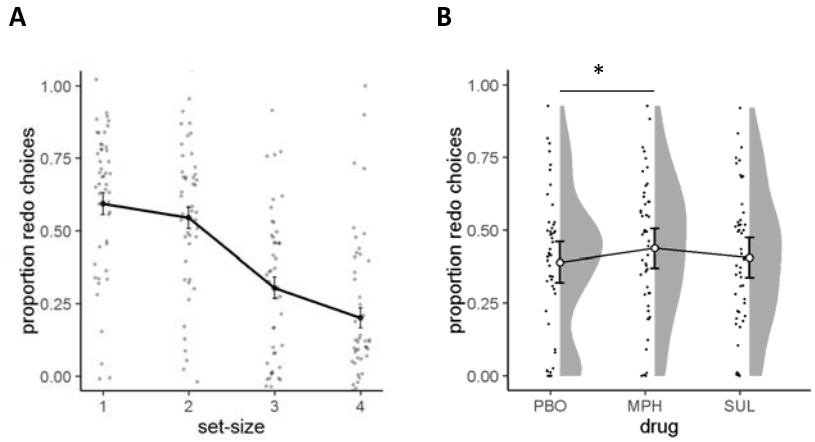

Figure 2. **A –** The proportion of trials on which participants chose the redo option as a function of set-size. Error bars represent standard error of the mean. **B –** The proportion of trials on which participants chose the redo option as a function of drug session. Individual data points and probability distribution [52]. Error bars represent 95% confidence interval around the mean (*: p < 0.05). MPH: methylphenidate; SUL: sulpiride; PBO: placebo. N = 49.

Effect of methylphenidate depended on baseline dopamine

As predicted, there was large individual variation in the direction and extent of drug effects on the proportion redo (Figure 2B). We assessed whether differences in baseline dopamine synthesis capacity could account for this variability.

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

Voxel-wise analyses revealed a significant positive correlation between midbrain dopamine and the methylphenidate effect on overall proportion redo (Figure 3C-D; Table S7). Thus, participants with higher midbrain dopamine exhibited greater methylphenidate-induced increases in proportion redo than participants with lower midbrain dopamine. Participants with the lowest baseline dopamine levels even exhibited a lower proportion redo after methylphenidate versus placebo. Although not significant, positive correlations with the methylphenidate effect were also found in the nucleus accumbens, putamen, and caudate nucleus. There was no association between the effect of sulpiride on proportion redo and baseline dopamine and no voxels correlated significantly with the difference in proportion redo between methylphenidate and sulpiride (Figure S4A-B; Table S7). The correlation between baseline dopamine and proportion redo under placebo was not significant (Figure 3A-B; Table S7).

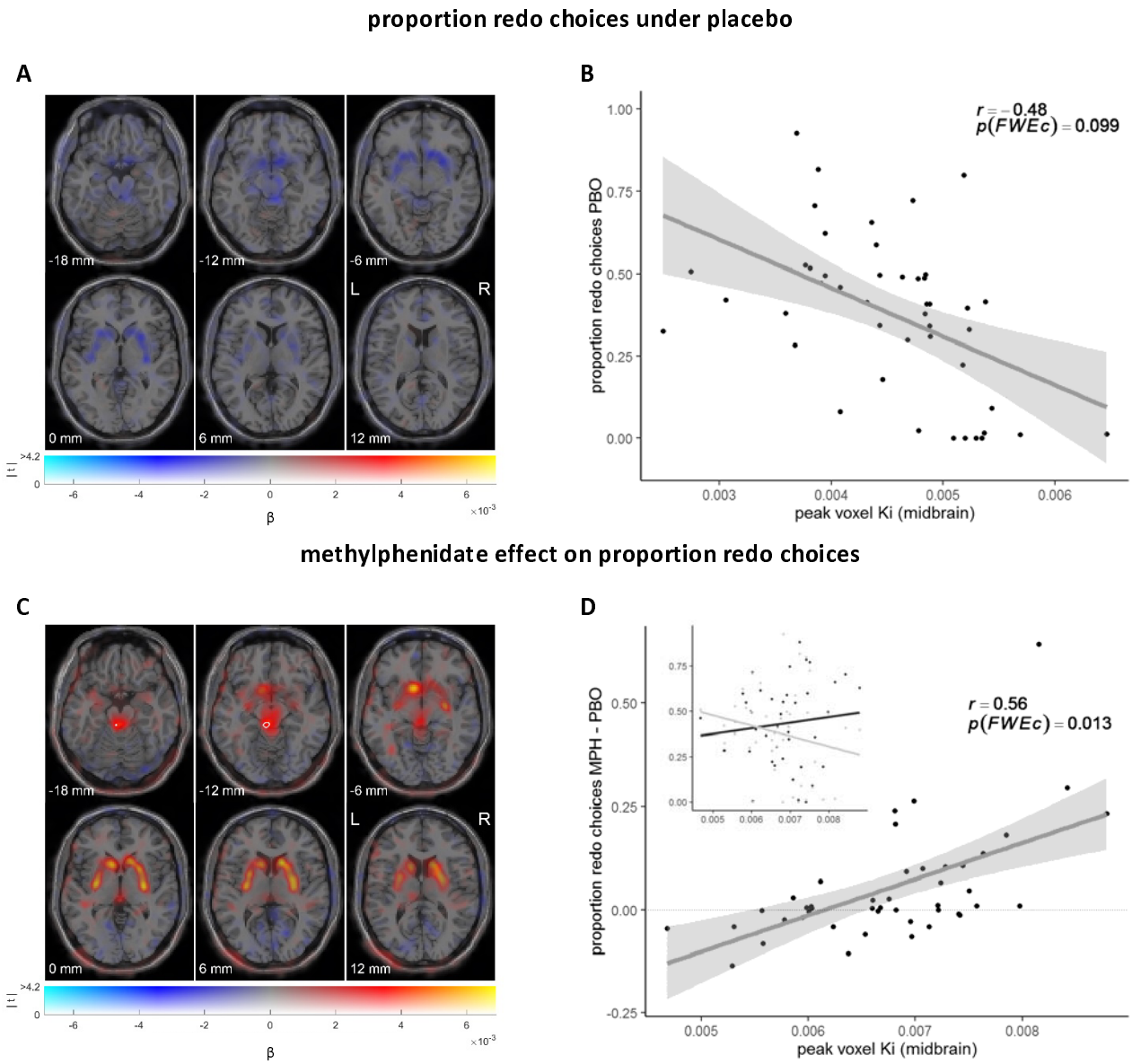

Figure 3. A – Voxels showing a positive (red) or negative (blue) regression coefficient on proportion redo on the placebo (PBO) session. **B –** Proportion redo on the placebo session plotted as a function of K_i value of the voxel that showed the strongest correlation with choice behavior on placebo (peak voxel K_i; located in the midbrain; MNI coordinates x = 6, y = -36, z = -14; see also Table S7). **C –** Voxels showing a positive (red) or negative (blue) regression coefficient on the effect of methylphenidate (MPH) on proportion redo. **D –** The effect of methylphenidate on proportion redo plotted as a function of the voxel that showed the strongest correlation with the MPH effect on choice behavior (peak voxel K_i; located in the midbrain; MNI coordinates x = -4, y = -32, z = -14; see also Table S7). Inset: proportion redo on placebo (grey) and methylphenidate (black) as a function of K_i. The cluster in the midbrain remains significant even after removing the participant exhibiting the greatest methylphenidate effect (t = 4.38, $p_{FWE\text{-}corrected}$ = 0.037 for MNI coordinates x = -4, y = -26, z = -12). The brain maps are dual-coded and simultaneously display the contrast estimate (x axis) and t values for the drug contrast (y axis). The

hue indicates the size of the contrast estimate, and the opacity indicates the height of the *t* value. Significant clusters (peak-level corrected, FWE, $p<0.05$) are encircled in white. The *z* coordinates correspond to the standard MNI brain. Neuroimaging data are plotted using a procedure introduced by Allen et al. [53] and implemented by Zandbelt [54]. Shaded area around the regression line represents 95% confidence interval. FWEc = corrected for family-wise error. $N = 46$.

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

Exploratory analyses revealed a set of clusters that correlated negatively with choice latency under placebo, in the left caudate nucleus and midbrain (Figure 4A-B; Table S7), indicating that higher baseline dopamine was associated with faster responding. The effect of methylphenidate correlated positively with baseline dopamine in the midbrain, left caudate nucleus and right putamen (Figure 4C-D; Table S7), indicating that methylphenidate slowed people with higher dopamine and invigorated people with lower dopamine. No significant correlation between baseline dopamine and the effect of sulpiride was observed and no voxels correlated significantly with the difference in choice latency on the methylphenidate and the sulpiride session (Figure S4C-D; Table S7). The drug-induced effects on motivation are positively correlated with the drug-induced effects on choice latency (Supplementary information).

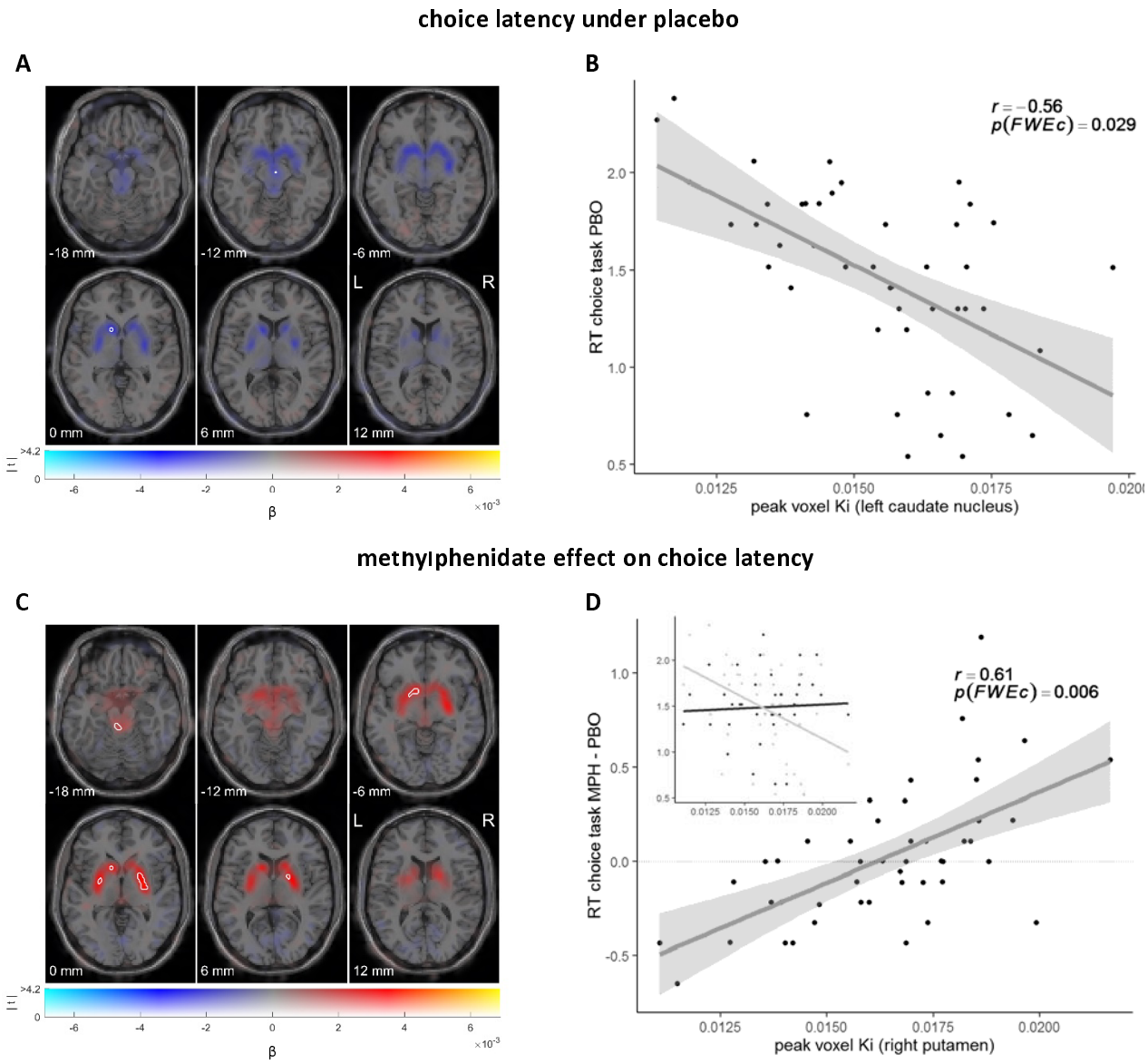

Figure 4. A – Voxels showing a positive (red) or negative (blue) regression coefficient on choice latency on the placebo (PBO) session. **B –** Choice latency on the placebo session plotted as a function of the voxel that showed the strongest correlation with choice latency on placebo (peak voxel K_i; located in the left caudate nucleus; MNI coordinates x = -10, y = 12, z = 0; see also Table S7). **C –** Voxels showing a positive (red) or negative (blue) regression coefficient on the effect of methylphenidate on choice latency. **D –** The effect of methylphenidate (MPH) on choice latency plotted as a function of the voxel that showed the strongest correlation with the MPH effect on choice latency (peak voxel K_i; located in the right putamen; MNI coordinates x = 28, y = -8, z = 0; see also Table S7). Inset: RT on placebo (grey) and methylphenidate (black) as a function of K_i. The brain maps are dual-coded and simultaneously display the contrast estimate (*x* axis) and *t* values for the drug contrast (*y* axis). The hue indicates the size of the contrast estimate, and the opacity indicates the height of the *t* value. Significant clusters (peak-level corrected, FWE, $p<0.05$) are encircled in white. The *z* coordinates correspond to the standard

MNI brain. Neuroimaging data are plotted using a procedure introduced by Allen et al. [53] and implemented by Zandbelt [54]. Shaded area around the regression line represents 95% confidence interval. $N = 46$.

Effect of methylphenidate depended on trait impulsivity

An exploratory Pearson's correlation analysis between trait impulsivity and the effect of methylphenidate on proportion redo revealed a significant positive association ($r = 0.38$, $p = 0.007$; Figure 5A), and a trending positive association between the effect of sulpiride and impulsivity ($r = 0.26$, $p = 0.070$; Figure 5B). Thus, methylphenidate increased the proportion redo to a greater degree in more impulsive participants. There was no correlation between impulsivity and proportion redo in the placebo sessions ($r = -0.10$, $p = 0.514$). A mediation analysis revealed that the association between trait impulsivity and the methylphenidate effect was fully mediated by midbrain dopamine (Figure 5C; Supplementary information).

There was also a strong significant negative correlation between choice latency on the placebo session and trait impulsivity ($r = -0.37$, $p = 0.009$), as well as a significant positive association between the effect of methylphenidate on choice latency and trait impulsivity ($r = 0.56$, $p < 0.001$; Figure 5D), and a trending positive association between the effect of sulpiride and impulsivity ($r = 0.26$, $p = 0.074$; Figure 5E). However, this relationship was only partly mediated by baseline dopamine (Figure 5F; Supplementary information).

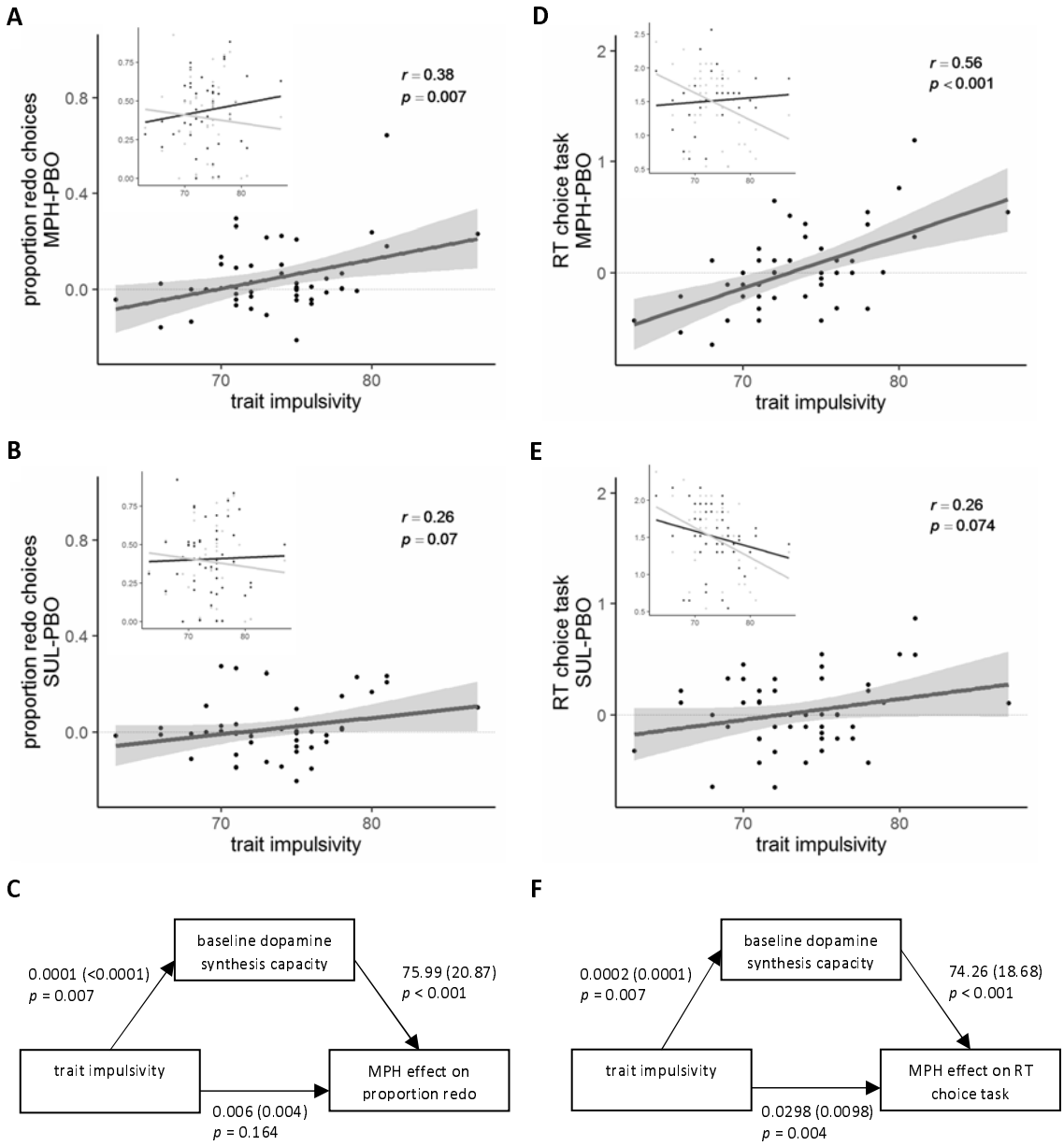

Figure 5. Drug induced effects as a function of trait impulsivity. **A –** The proportion of trials on which participants chose the higher demand redo option under methylphenidate (MPH) minus the proportion of trials on which participants chose the redo option under placebo (PBO) as a function of impulsivity. The correlation is still significant without the participant with the greatest methylphenidate effect (r = 0.29, p = 0.042). **B –** The proportion of trials on which participants chose the redo option under sulpiride (SUL) minus the proportion of trials on which participants chose the redo option under placebo as a function of impulsivity. Insets: Proportion redo on placebo (grey) and drug (black) as a function of impulsivity. **C** – Schematic diagram of mediation analysis results. Dopamine synthesis capacity fully mediates the relationship between trait impulsivity and the effect of methylphenidate on proportion redo. Path values are unstandardized regression coefficients (standard error). **D.** Median choice latency

under methylphenidate minus median choice latency under placebo as a function of impulsivity. **E –** Median choice latency under sulpiride minus median choice latency under placebo as a function of impulsivity. Insets: Choice latency on placebo (grey) and drug (black) as a function of impulsivity. **F** – Schematic diagram of mediation analysis results. Dopamine synthesis capacity partially mediates the relationship between trait impulsivity and the effect of methylphenidate on latency. Path values are unstandardized regression coefficients (standard error). *N* = 49 for **A**,**B**,**D**,**E** and *N* = 46 for **C, F**. Shaded areas represents 95% confidence interval.

DISCUSSION

The present study demonstrates that, as predicted, the effects of methylphenidate on cognitive motivation in healthy volunteers depend on individual differences in baseline dopamine synthesis capacity. Methylphenidate increased cognitive motivation to a greater extent in people with high baseline dopamine than in people with low baseline dopamine. Our data firmly establish the pervasive baseline-dependency hypothesis of individual variability in the efficacy of the most commonly used catecholaminergic drug, methylphenidate. While this hypothesis has been around for a long time, so far only indirect evidence in its support has been obtained from studies employing putative proxies of baseline dopamine levels [23, 55, 56] or dopamine receptor availability [13, 23]. Further, these studies investigated performance, rather than motivation. The present experimental design provides a particularly good test of drug-induced changes in participants' cognitive motivation, as opposed to changes in cognitive capacity, because methylphenidate was administered after the task performance phase, but before the discounting phase. Our findings demonstrate unequivocally that higher-dopamine participants exhibit greater methylphenidate-related increases in cognitive motivation that cannot be accounted for by changes in performance. This result concurs generally with dopamine's strong implication in cognitive motivation [19, 57] as well as, indirectly, with motivational or energetic accounts of ADHD symptoms [58–60].

Greater beneficial effects on cognitive motivation were observed in participants with higher trait impulsivity. This is in line with the classic rate-dependency hypothesis [26, 61] and the therapeutic effects of methylphenidate in ADHD. Critically, the current study provides a mechanistic account of this observation by establishing that this link between trait impulsivity and methylphenidate's motivational efficacy is fully mediated by dopamine synthesis capacity. The relationship between trait impulsivity and dopamine synthesis capacity itself is not surprising given our previous observation that disorders associated with impulsivity are also accompanied by increased dopamine synthesis capacity [51, 62], although there are also discrepant findings [63, 64]. The finding that methylphenidate increased choice latency in high impulsive participants, while invigorating low impulsive participants, concurs with the clinically relevant observation that psychostimulants can have contrasting calming versus stimulating effects in people with ADHD and healthy people suffering from fatigue, respectively [28, 29]. The key implication of these findings is that higher impulsive people exhibit greater beneficial effects of methylphenidate because they have higher dopamine synthesis capacity. In the Supplementary information, we speculate that, unlike a previous study [18], the present study succeeded in uncovering clinically relevant motivational enhancing effects of methylphenidate in high impulsive participants, because the task required choices between effort versus rest (leisure), rather than between high versus low effort.

One limitation of the current large pharmacological PET study is that it does not allow us to directly address the neural locus of methylphenidate's effect. The finding that sub-threshold correlations were present in the nucleus accumbens and caudate nucleus 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. A 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 baseline-dependent effects of methylphenidate on cognitive motivation.

The finding that the effects of methylphenidate, which blocks both dopamine and noradrenaline transporters [65, 66], were not accompanied by significant effects of the selective D2 receptor antagonist sulpiride (Supplementary information) might also lead some to ask whether they reflect modulation of noradrenaline instead of dopamine [67–71]. However, we cannot exclude the possibility that the sulpiride manipulation was ineffective, given a lack of subjective or physiological effect of sulpiride (Supplemental information). Given that methylphenidate's effects depended on [^{18}F]DOPA uptake in the midbrain, extending into the dorsal striatum, which does not contain any noradrenaline receptors, we argue that the effects 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 [25] .

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

References

1. Duverne S, Koechlin E. Hierarchical Control of Behaviour in Human Prefrontal Cortex. In: Egner T, editor. Wiley Handb. Cogn. Control, Chichester: Wiley & Sons, Ltd; 2017. p. 207–221.
2. Arnsten AFT, Wang M, Paspalas CD. Dopamine ' s Actions in Primate Prefrontal Cortex: Challenges for Treating Cognitive Disorders. 2015:681–696.
3. Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry. 2011;69:e113–e125.
4. Goldman-Rakic PS. The cortical dopamine system: role in memory and cognition. Adv Pharmacol. 1997;42:707–711.
5. Arnsten AT, Plizska SR. Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit hyperactivity disorder and related disorders. Pharmocological Biochem Behav. 2011;99:211–216.
6. Prince J. Catecholamine dysfunction in attention-deficit/hyperactivity disorder an update. J Clin Psychopharmacol. 2008;28:39–45.
7. Greely H, Campbell P, Sahakian B, Harris J, Kessler RC, Gazzaniga M, et al. Towards responsible use of cognitive-enhancing drugs by the healthy. Nature. 2008:235–245.
8. Husain M, Mehta MA. Cognitive enhancement by drugs in health and disease. Trends Cogn Sci. 2011;15:28–36.
9. Schelle KJ, Olthof BMJ, Reintjes W, Bundt C, Gusman-Vermeer J, Vanmil ACCM. A survey of substance use for cognitive enhancement by university students in the Netherlands. Front Syst Neurosci. 2015;9:1–11.

10. Elliott R, Sahakian BJ, Matthews K, Bannerjea A, Rimmer J, Robbins TW. Effects of methylphenidate on spatial working memory and planning in healthy young adults. Psychopharmacology (Berl). 1997;131:196–206.

11. Fallon SJ, van der Schaaf ME, ter Huurne N, Cools R. The Neurocognitive Cost of Enhancing Cognition with Methylphenidate: Improved Distractor Resistance but Impaired Updating. J Cogn Neurosci. 2017;29:652–663.

12. Rogers RD, Blackshaw AJ, Middleton HC, Matthews K, Hawtin K, Crowley C, et al. Tryptophan depletion impairs stimulus-reward learning while methylphenidate disrupts attentional control in healthy young adults: Implications for the monoaminergic basis of impulsive behaviour. Psychopharmacology (Berl). 1999;146:482–491.

13. Samanez-Larkin G, Buckholtz J. A thalamocorticostriatal dopamine network for psychostimulant-enhanced human cognitive flexibility. Biol …. 2013;74:99–105.

14. Spronk DB, van Wel JHP, Ramaekers JG, Verkes RJ. Characterizing the cognitive effects of cocaine: A comprehensive review. Neurosci Biobehav Rev. 2013;37:1838–1859.

15. Ter Huurne N, Fallon SJ, Van Schouwenburg M, Van Der Schaaf M, Buitelaar J, Jensen O, et al. Methylphenidate alters selective attention by amplifying salience. Psychopharmacology (Berl). 2015;232:4317–4323.

16. Kool W, Botvinick M. The intrinsic cost of cognitive control. Behav Brain Sci. 2013;36:697–698; discussion 707-726.

17. Clark CR, Geffen GM, Geffen LB. Role of monoamine pathways in attention and effort: Effects of clonidine and methylphenidate in normal adult humans. Psychopharmacology (Berl). 1986;90:35–39.

18. Froböse MI, Swart JC, Cook JL, Geurts DEM, Den Ouden HEM, Cools R. Catecholaminergic modulation of the avoidance of cognitive control. J Exp Psychol Gen. 2018;147:1763–1781.

19. Mcguigan S, Zhou S, Brosnan B, Thyagarajan D, Bellgrove MA, Chong T-J. Dopamine restores cognitive motivation in Parkinson ' s disease. 2019:719–732.

20. Wardle MC, Treadway MT, Mayo LM, Zald DH, de Wit H. Amping Up Effort: Effects of d-Amphetamine on Human Effort-Based Decision-Making. J Neurosci. 2011;31:16597–16602.

21. Hosking JG, Floresco SB, Winstanley CA. Dopamine antagonism decreases willingness to expend physical, but not cognitive, effort: A comparison of two rodent cost/benefit decision-making tasks. Neuropsychopharmacology. 2015;40:1005–1015.

22. Cocker PJ, Hosking JG, Benoit J, Winstanley CA. Sensitivity to cognitive effort mediates psychostimulant effects on a novel rodent cost/benefit decision-making task. Neuropsychopharmacology. 2012;37:1825–1837.

23. Clatworthy PL, Lewis SJG, Brichard L, Hong YT, Izquierdo D, Clark L, et al. Dopamine release in dissociable striatal subregions predicts the different effects of oral methylphenidate on reversal learning and spatial working memory. J Neurosci. 2009;29:4690–4696.

24. Cools R, Sheridan M, Jacobs E, D'Esposito M. Impulsive Personality Predicts Dopamine-Dependent Changes in Frontostriatal Activity during Component Processes of Working Memory. J Neurosci. 2007;27:5506–5514.

25. Del Campo N, Fryer TD, Hong YT, Smith R, Brichard L, Acosta-Cabronero J, et al. A positron emission tomography study of nigro-striatal dopaminergic mechanisms underlying attention: Implications for ADHD and its treatment. Brain. 2013;136:3252–3270.

26. Dews PB. Studies on behavior. IV. Stimulant actions of methamphetamine. J Pharmacol Exp Ther. 1958;122:137–147.

27. Lyon M, Robbins TW. The action of central nervous system drugs: a general theory concerning amphetamine effects. In: Essman W, editor. Curr. Dev. Psychopharmacol., New York: Spectrum Publications; 1975. p. 80–163.

28. Rapoport JL, Buchsbaum MS, Weingartner H, Zahn TP, Ludlow C, Mikkelsen EJ. Dextroamphetamine: Its Cognitive and Behavioral Effects in Normal and Hyperactive Boys and Normal Men. Arch Gen Psychiatry. 1980;37:933–943.

29. Koelega HS. Stimulant drugs and vigilance performance: a review. Psychopharmacology (Berl). 1993;111:1–16.

30. Egerton A, Demjaha A, McGuire P, Mehta MA, Howes OD. The test-retest reliability of 18F-DOPA PET in assessing striatal and extrastriatal presynaptic dopaminergic function. Neuroimage. 2010;50:524–531.

31. Schabram I, Henkel K, Shali SM, Dietrich C, Schmaljohann J, Winz O, et al. Acute and sustained effects of methylphenidate on cognition and presynaptic dopamine metabolism: An [18F]FDOPA PET study. J Neurosci. 2014;34:14769–14776.

32. Hall H, Sedvall G, Magnusson O, Kopp J, Halldin C, Farde L. Distribution of D1- and D2-dopamine receptors, and dopamine and its metabolites in the human brain. Neuropsychopharmacology. 1994;11:245–256.

33. Mehta MA, Mcgowan SW, Lawrence AD, Aitken MRF, Montgomery AJ, Grasby PM. Systemic sulpiride modulates striatal blood flow: relationships to spatial working memory and planning. 2003;20:1982–1994.

34. Westerink BHC, Kawahara Y, De Boer P, Geels C, De Vries JB, Wikström H V., et al. Antipsychotic drugs classified by their effects on the release of dopamine and noradrenaline in the prefrontal cortex and striatum. Eur J Pharmacol. 2001;412:127–138.

35. Bardgett ME, Depenbrock M, Downs N, Points M, Green L. Dopamine Modulates Effort-Based Decision-Making in Rats. Behav Neurosci. 2009;123:242–251.

36. Burke CJ, Soutschek A, Weber S, Raja Beharelle A, Fehr E, Haker H, et al. Dopamine Receptor-Specific Contributions to the Computation of Value. Neuropsychopharmacology. 2018;43:1415–

1424.

37. Nowend KL, Arizzi M, Carlson BB, Salamone JD. D1 or D2 antagonism in nucleus accumbens core or dorsomedial shell suppresses lever pressing for food but leads to compensatory increases in chow consumption. Pharmacol Biochem Behav. 2001;69:373–382.

38. Pardo M, Lopez-Cruz L, Valverde O, Ledent C, Baqi Y, Müller CE, et al. Adenosine A 2A receptor antagonism and genetic deletion attenuate the effects of dopamine D 2 antagonism on effort-based decision making in mice. Neuropharmacology. 2012;62:2068–2077.

39. Salamone JD, Steinpreis RE, McCullough LD, Smith P, Grebel D, Mahan K. Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food choice procedure. Psychopharmacology (Berl). 1991;104:515–521.

40. Wade TR, De Wit H, Richards JB. Effects of dopaminergic drugs on delayed reward as a measure of impulsive behavior in rats. Psychopharmacology (Berl). 2000;150:90–101.

41. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods. 2009;41:1149–1160.

42. Cools R. The costs and benefits of brain dopamine for cognitive control. Wiley Interdiscip Rev Cogn Sci. 2016;7:317–329.

43. Papadopetraki D, Froböse MI, Westbrook A, Zandbelt BB, Cools R. Quantifying the cost of cognitive stability and flexibility. BioRxiv 743120. 2019. 2019. https://doi.org/https://doi.org/10.1101/743120.

44. Westbrook A, Kester D, Braver TS. What Is the Subjective Cost of Cognitive Effort? Load, Trait, and Aging Effects Revealed by Economic Preference. PLoS One. 2013;8:1–8.

45. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. J Cereb Blood Flow Metab. 1983;5:584–590.

46. Morey RD, Rouder JN. BayesFactor: Computation of Bayes Factors for Common Designs. 2018.

47. Makowski D, Ben-Shachar, M. S. Lüdecke D. Understand and Describe Bayesian Models and Posterior Distributions using bayestestR. 2019.

48. Team RC. R: A language and environment for statistical computing. 2018.

49. Sescousse G, Ligneul R, van Holst RJ, Janssen LK, de Boer F, Janssen M, et al. Spontaneous eye blink rate and dopamine synthesis capacity: preliminary evidence for an absence of positive correlation. Eur J Neurosci. 2018;47:1081–1086.

50. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol. 1995;51:768–774.

51. Holst RJ Van, Sescousse G, Janssen LK, Janssen M, Berry AS, Jagust WJ, et al. Increased Striatal Dopamine Synthesis Capacity in Gambling Addiction. Biol Psychiatry. 2018;83:1036–1043.

52. Allen M, Poggiali D, Whitaker K, Marshall T, Kievit R. RainCloudPlots tutorials and codebase (Version v1.1). Zenodo. 2018.

53. Allen EA, Erhardt EB, Calhoun VD. Data visualization in the neurosciences: overcoming the curse of dimensionality. Neuron. 2012;74:603–608.

54. Zandbelt B. Slice display. figshare. 2017.

55. Cools R, Altamirano L, D'Esposito M. Reversal learning in Parkinson's disease depends on medication status and outcome valence. Neuropsychologia. 2006;44:1663–1673.

56. Van Der Schaaf ME, Van Schouwenburg MR, Geurts DEM, Schellekens AFA, Buitelaar JK, Verkes RJ, et al. Establishing the dopamine dependency of human striatal signals during reward and punishment reversal learning. Cereb Cortex. 2014;24:633–642.

57. Aarts E, van Holstein M, Cools R. Striatal dopamine and the interface between motivation and cognition. Front Psychol. 2011;2:1–11.

58. Chelonis JJ, Johnson TA, Ferguson SA, Berry KJ, Kubacak B, Edwards MC, et al. Effect of

Methylphenidate on Motivation in Children With Attention-Deficit/Hyperactivity Disorder. Exp Clin Psychopharmacol. 2011;19:145–153.

59. Sergeant J. The cognitive-energetic model: an empirical approach to Attention-Deficit Hyperactivity Disorder. Neurosci Biobehav Rev. 2000;24:7–12.

60. Volkow ND, Wang G, Newcorn JH, Scott H, Wigal TL, Telang F, et al. Motivation Deficit in ADHD is Associated with Dysfunction of the Dopamine Reward Pathway. Mol Psychiatry. 2011;16:1147–1154.

61. Sahakian BJ, Robbins TW. ARE THE EFFECTS OF PSYCHOMOTOR STIMULANT DRUGS ON HYPERACTIVE CHILDREN REALLY PARADOXICAL? Med Hypotheses. 1977;3:154–158.

62. Lawrence AD, Brooks DJ. Ventral striatal dopamine synthesis capacity is associated with individual differences in behavioral disinhibition. Front Behav Neurosci. 2014;8:1–6.

63. Ernst M, Zametkin AJ, Matochik JA, Jons PH, Cohen RM. Dopa decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18]fluorodopa positron emission tomographic study. J Neurosci. 1998;18:5901–5907.

64. Hammes J, Theis H, Giehl K, Hoenig MC, Greuel A, Tittgemeyer M, et al. Dopamine metabolism of the nucleus accumbens and fronto-striatal connectivity modulate impulse control. Brain. 2019;142:733–743.

65. Kuczenski R, Segal DS. Locomotor effects of acute and repeated threshold doses of amphetamine and methylphenidate: relative roles of dopamine and norepinephrine. J Pharmacol Exp Ther. 2001;296:876–883.

66. Scheel-Krüger J. Comparative studies of various amphetamine analogues demonstrating different interactions with the metabolism of the catecholamines in the brain. Eur J Pharmacol. 1971;14:47–59.

67. Aston-Jones G, Cohen JD. Adaptive gain and the role of the locus coeruleus-norepinephrine

system in optimal performance. J Comp Neurol. 2005;493:99–110.

68. Gilzenrat MS, Nieuwenhuis S, Jepma M, Cohen JD. Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. Cogn Affect Behav Neurosci. 2010;10:252–269.

69. Hopstaken JF, van der Linden D, Bakker AB, Kompier MAJ. The window of my eyes: Task disengagement and mental fatigue covary with pupil dynamics. Biol Psychol. 2015;110:100–106.

70. Rajkowski J, Kubiak P, Aston-Jones G. Correlations between locus coeruleus (LC) neural activity, pupil diameter and behavior in monkey support a role of LC in attention. Soc Neurosci Abstr. 1993;19:974.

71. Van den Brink RL, Murphy PR, Nieuwenhuis S. Pupil Diameter Tracks Lapses of Attention. PLoS One. 2016:1–16.