Effects of methylphenidate on reversal learning depend on working memory capacity

Mojtaba Rostami Kandroodi^{1,2*}, Jennifer L. Cook³, Jennifer C. Swart², Monja I. Froböse², Dirk E.M. Geurts^{2,4}, Abdol-Hossein Vahabie⁵, Majid Nili Ahmadabadi¹, Roshan Cools^{2,4+}, Hanneke E.M. den Ouden^{2*+}

¹ School of Electrical and Computer Engineering, University of Tehran, Tehran, Iran

² Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands

³ School of Psychology, University of Birmingham, Birmingham, United Kingdom

⁴ Department of Psychiatry, Radboud University Medical Centre, Nijmegen, The Netherlands

⁵ School of Cognitive Sciences, Institute for Research in Fundamental Sciences (IPM), Tehran, Iran

⁺ These authors contributed equally to this work

^{*} Corresponding authors: mojtaba.rostami@ut.ac.ir and h.denouden@donders.ru.nl

Abstract- Brain catecholamines have long been implicated in cognitive flexibility, exemplified by catecholamine drug and genetic effects on probabilistic reversal learning. However, the mechanisms underlying such effects are unclear. Here we investigated effects of an acute catecholamine challenge with methylphenidate (20 mg, oral) on a novel probabilistic reversal learning paradigm with three options, which was designed to disentangle effects on punishment avoidance from effects on reward perseveration. Given the known large individual variability in methylphenidate's effects, we stratified our effects by working memory capacity and trait impulsivity, putative proxies of baseline dopamine, in a large sample ($n = 102$) of healthy volunteers. Contrary to our prediction, methylphenidate did not alter performance in the reversal phase of the task. However, learning rates during the initial acquisition phase of the task were altered by methylphenidate, in a manner that depended on baseline working memory capacity. Participants with greater capacity exhibited greater adaptive reduction of the learning rate in this initial phase, in which outcome contingencies were stable. We hypothesize that the addition of a third choice option in this novel paradigm increased the demands for reinforcement learning, uncovering an effect of methylphenidate on initial learning rather than flexibility to reverse what was learnt.

Keywords- reversal learning; methylphenidate; catecholamines; dopamine; working memory; computational modelling of behaviour.

INTRODUCTION

Brain catecholamines are well known to play a fundamental role in reinforcement learning and decision-making. Most notably, in the last two decades, a wealth of studies have shown that dopaminergic midbrain firing increases when experience exceeds expectations (Fiorillo et al. 2003; Montague et al. 1996; Schultz 2016). This dopaminergic signaling is widely accepted to function as a teaching signal driving reinforcement learning (Niv and Montague 2017). Dopamine has also been implicated in the ability to flexibly adjust behaviour to changing environments (e.g. Boulougouris et al. 2009; Chudasama and Robbins 2006; Clarke et al. 2011; Clatworthy et al. 2009; Cools et al. 2001; Cools and D'Esposito 2011; Dodds et al. 2008; Groman et al. 2012; den Ouden et al. 2013; Swainson et al. 2000). For example, we have previously shown that genetic variability in the dopamine transporter DAT1 predicts the influence of prior choice history on the ability to update a learnt association when the environment has changed (den Ouden et al. 2013). In the present study, we assess the causal role of the catecholamines through pharmacological manipulation with the catecholamine transporter blocker methylphenidate. Methylphenidate acts by blocking dopamine and noradrenaline transporters (DAT/NAT), which increases extracellular catecholamine availability in the synaptic cleft, without stimulating release or acting as a receptor (ant)agonist (e.g. Volkow et al. 2002). It is thought to prolong the effect of both dopamine and noradrenaline release, as reuptake is slowed (Berridge et al. 2006; Madras et al. 2005).

In addition to establishing the causal role of the catecholamines in perseverative behavior during reversal learning, we also aimed to elucidate the specific processes that are altered by the catecholamines contributing to increased perseverative behaviour. Specifically, perseveration may result from either a 'stamping in' of rewarded behaviour, leading to an inability to 'let go' of responding to a previously rewarded stimulus, or changed ability to approach a previously punished stimulus (i.e. 'punishment avoidance'). Here, we introduce a novel reversal learning paradigm to dissociate these two alternatives, through addition of a novel 'neutral' response option. Based on our previous finding that natural genetic *DAT1* variation was associated with a stronger correlation between reinforcement history and perseveration (den Ouden et al. 2013), we hypothesized that methylphenidate would alter perseverative behavior, specifically by inducing an inability to 'let go' of a responding to a previously rewarded stimulus rather than by impairing punishment-based learning (Cools et al. 2006; Frank et al. 2004).

Previous studies have shown that there is large inter-task and inter-individual variability in catecholaminergic drug effects on cognitive task performance (Kimberg et al. 1997; Cools et al. 2007; Van Der Schaaf et al. 2013; Linssen et al. 2014; Swart et al. 2017; Froböse et al. 2018; Cook et al. 2019), including probabilistic reversal learning (Clatworthy et al. 2009). Given that methylphenidate prolongs the effects of catecholamine release by blocking the reuptake of catecholamines, it is likely that the effect of methylphenidate on catecholamine-dependent function is a function of dopamine synthesis capacity and release. Simply put, if there is no release, there is no reuptake to block. To take into account the established large individual variability in methylphenidate effects, we stratified our drug effects by two measures that have been previously demonstrated to relate to baseline dopamine function: working memory (WM) span for its relation to striatal dopamine synthesis capacity (Cools et al. 2008; Landau et al. 2009) and trait impulsivity for its relation to dopamine (auto)receptor availability

(Buckholtz et al. 2010; Kim et al. 2013; Lee et al. 2009; Reeves et al. 2012), and collected a large sample (N = 102) to expose individual differences.

METHODS

General procedure and pharmacological intervention

The study consisted of two test sessions with an interval of one week to two months. The first test day started with informed consent, followed by a medical screening. Participation was discontinued if participants met any of the exclusion criteria (*Supplemental methods 1*). On both test days, participants first completed baseline measures, as well as the Instrumental and Pavlovian phases of the Pavlovian-Instrumental transfer (PIT) task (Geurts et al. in prep). Participants received a capsule containing either 20 mg methylphenidate (Ritalin®, Novartis) or placebo, in a double-blind, placebo-controlled, cross-over design. Methylphenidate blocks the dopamine and noradrenaline transporters, thereby diminishing the reuptake of catecholamines. When administered orally, methylphenidate has a maximal plasma concentration after 2 hours and a plasma half-life of 2-3 hours (Kimko et al. 1999). Below we denote capsule intake as $t = 0$.

The probabilistic reversal learning task was the last task participants completed following capsule intake, at $t = 186.1$ (7.9) min, mean(st.d.), which is well within the peak of plasma concentration. This task was preceded by 5 other tasks published elsewhere (*Figure 1*). Both test days lasted approximately 4.5 hours, which participants started at the same time of day (maximum difference of 45 minutes). Blood pressure, mood and potential medical symptoms were monitored three times each day: before capsule intake $t = -5.3$ (1.7) min, directly prior to start of the task battery $t = 47.4$ (7.6) and after finishing the task battery $t = 190.9$ (7.9). Exact mood and medical symptom ratings are described in supplemental methods 2. Participants were instructed to abstain from alcohol and recreational drugs 24h prior to testing and from smoking and drinking coffee on the days of testing. Participants completed self-report questionnaires at home between (but not on) test days. Upon completion of the study, participants received a monetary reimbursement or study credits for participation. The study was in line with the local ethical guidelines approved by the local ethics committee (CMO / METC Arnhem Nijmegen: protocol NL47166.091.13), pre-registered (trial register NTR4653, <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4653>), and in accordance with the Helsinki Declaration of 1975.

Participants

106 healthy, young adults participated in this study and were recruited via flyers around the campus and the digital participant pool of the Radboud University, Nijmegen. All participants were native Dutch speakers and provided written informed consent to participate in the study. Exclusion criteria comprised a history of psychiatric, neurological or endocrine disorders. A complete overview of the exclusion criteria can be found in the supplemental methods 1. Data from four participants could not be collected on day 2 due to medical reasons (mild arrhythmia: $n = 1$, elevated heart rate and nausea: $n = 1$), and drop-outs ($n = 2$). Thus, the analyses include 102 adult participants (aged 18-28 years, mean age = 21.5, st.d. = 2.3, 51 women, 81 right-handed), where 50 participants received methylphenidate

on the first testing session. Additional demographic information, and results from baseline neuropsychological assessment and self-report questionnaires of included participants are reported in *Table 1*.

A - Study Timeline

B - Reversal Learning design

C - Trial-by-trial choice

D - Average choice probability

E - Feedback sensitivity

Figure 1. Experimental Design and basic results. **A.** Study timeline. Participants took part in 2 sessions, where on day 1 they started with a 20 min. medical screening and on day 2 took the Listening span test. Neuropsychological questionnaires (Quest) were completed at home between the two sessions. Mood and medical symptom ratings (MMSR) were acquired at 3 time points. A battery of 6 tasks (Cook et al. 2019; Froböse et al. 2018; Swart et al. 2017) was performed in a fixed order, where the probabilistic reversal learning (PRL) task was always performed last. Average timings are indicated, with timings most relevant for the current study in purple. **B.** Reversal learning design. On each trial, three visual stimuli were represented in three out of four randomly selected locations. Participants had to choose one of the stimuli with a mouse click and subsequently received feedback. The feedback would either be a reward (green, happy emotion) and punishment (red, sad emotion). During acquisition, the rewarded stimulus (here purple) resulted in a 75:25 ratio of reward/punishment. Selecting the neutral stimulus (orange), and punished stimulus (blue) led to 50:50 and 25:75 ratio of reward/punishment, respectively. After 40 trials, the reversal phase started, and rewarded and punished stimulus contingencies reversed. The participant now had to learn to select the blue stimulus. **C.** Trial-by-trial choice. Trial-by-trial averaged probability of selection of each stimulus. A sliding window with 5-trial width is used for smoothing. Overall, participants learned to make the correct selection for each of the phases, and showed relatively rapid reversal. **D.** Average choice probability.

Distribution of choice probability averaged within acquisition (dark blue) and reversal (light blue) phases. In both phases participants learnt to select 75% rewarded option, but do significantly less well during the reversal phase. E. Feedback sensitivity. The degree to which people repeated a choice was modulated by the valence of the previous outcome for that choice: People were more likely to reselect a stimulus ('stay') after it had been rewarded than after it was punished. This effect was weaker during the reversal phase (less stay after a win, more stay after a loss), in line with slower learning during reversal. Note that the intercept in this plot was chance level stay (1/3); even after a loss people were more likely to stay than chance (simple effect of pStay following loss: $F(1,99) = 77.1$; $p < .0001$, following win $F(1,99) = 1603.4$; $p < .0001$), reflecting a relatively small impact of a single (negative) outcome, and thus slow learning.

Probabilistic Reversal Learning task

Participants performed a probabilistic reversal learning (PRL) task with three choice options in each trial. This task is an adjusted version of (den Ouden et al. 2013), which consisted of 2 cues which were predominantly rewarded or predominantly punished. We here added a neutral stimulus (with 50-50% contingencies). The task contains 80 trials. On each trial, three visual stimuli $\{S_1, S_2, S_3\}$ were represented in three out of four randomly selected locations (left, right, top, or bottom of the screen). Participants had to choose one of the stimuli with a mouse click and subsequently received feedback. There was no time limit for the responses. The feedback would either be a reward (green, happy emotion) and punishment (red, sad emotion), see *Figure 1B*. In order to maximize reward, participants had to learn by trial-and-error to choose the mostly rewarded stimulus. Choosing the rewarded stimulus, S_1 , (defined as the first stimulus that was chosen by the participant) gives reward/punishment with contingencies of 75:25. The punished stimulus, S_2 , results in reward/punishment with the opposite (25:75) contingency ratio. Thus, for S_1 and S_2 stimuli, on 25% of trials participants received 'misleading' feedback. After 40 trials the reinforcement contingencies reversed, so that the mostly rewarded stimulus now became mostly punished and vice versa. Thus, the task consisted of an acquisition and a reversal phase. The third stimulus, S_3 , is 'Neutral', as its selection results in 50:50 ratio reward/punishment throughout the task. The feedback for each stimulus type is generated as a pseudorandom and fixed series during each phase. Feedback for the selected stimulus was determined in a serial manner according to the action sequence of the participant. Participants were instructed that the contingency rules would change once or more frequently. They were also informed that the feedback only depends on which stimulus they choose, and not on the location of the stimulus nor on their previous choices.

Behavioural data analysis

Data quality Assessment

A priori we decided to exclude any participant who selected the same stimulus the entire experiment as they likely did not understand the task (cf. den Ouden et al. 2013). However, this did not happen in the current sample. Trials with RT faster than 200 ms. likely reflect responses that were not based on a deliberate choice between the stimuli. We confirm that results do not change whether these trials are included (main article) or excluded (supplemental results & discussion 1).

Accuracy

The statistics software SPSS (version 22) was used to analyze the raw behavioural data. The percentage of choosing each action was calculated across acquisition and reversal phases. The basic design of this analysis was a 2x2 factorial ANOVA with factors Task Phase (acquisition / reversal) and Valence (probability of choosing the 75% Rewarded, or 75% Punished stimulus). Note that these are rendered relatively independent by including the neutral stimulus which is the implicit baseline in this analysis. This analysis allowed us to assess changes in performance specific to the reversal phase, independently of overall changes in learning, which would point to a change in perseverative behaviour. Furthermore, the Valence interaction assesses the effects on perseveration due to the 'stamping in' of reward (worse performance due to a continuation of selection of the now-punished S_1 during the reversal phase) versus the punishment avoidance hypothesis (worse performance due to failure to select the previously punished but now rewarded S_2).

To assess the effect of methylphenidate on performance, this basic design was extended with the factor Drug, resulting in a three-way repeated measure ANOVA with Valence (Rewarded, Punished), Phase (acquisition, reversal) and Drug (methylphenidate, placebo) included as within-subject factors. Furthermore, Listening Span total score and Barratt Impulsiveness Score were added as covariates of interest. For reporting significant results, the Huynh-Feldt correction was used when significant non-sphericity was detected.

Win-Stay Lose-Shift

We next assessed trial-by-trial behavioural adjustment following rewards and punishments, reflecting (instantaneous) learning. This is reflected in the tendency to select the same stimulus or instead to shift to a different stimulus, following either a win (win-stay) or a loss (lose-shift). Note that chance level probability to shift is 2/3 and to stay is 1/3, given that there are always 3 stimulus options. Therefore, we computed the proportion of stay after win and after loss, $p(stay|win)$ and $p(stay|loss)$, for which chance level is 1/3. We subtract 1/3 from all scores to allow us to interpret the intercept as a deviation from chance performance. We conducted a three-way repeated-measures ANOVA with factors Outcome (win, loss), Phase (acquisition, reversal) and Drug (methylphenidate, placebo), again with Listening Span total score and Barratt Impulsiveness total score as covariates.

Control analyses of effects of no interest

To verify that our findings are not confounded by covariates (age, Nederlandse Leestest voor Volwassenen (NLV); Dutch adult reading test; a measure of verbal intelligence) and factors (gender, testing order) of no interest, we repeated the analyses above including these covariates and factors and confirmed that significant results remained significant, and non-significant results remained non-significant (Supplemental results & discussion 1).

Computational Modeling

We employed a computational modelling approach to quantify and compare latent mechanisms underlying the behaviour of participants, and particularly the effects of methylphenidate on behaviour as a function of working memory capacity. For this, we augmented a previously established model of a simpler variant of this reversal learning task (den Ouden et al. 2013), and subsequently assessed effects of methylphenidate on the various parameters in this model, as described below.

Model space

Our model space comprised four models. The first model (M1), known as the Experience-Weighted Attraction model (EWA) (Camerer and Ho 1999), and is an extended version of a standard reinforcement learning (RL) model. We have previously shown that this model can capture (variability in) perseverative behaviour in a simpler version of the current paradigm (den Ouden et al. 2013). The key feature of this model is the so-called experience-weight parameter, which models the increasing impact of past experience on subsequent decisions. With increasing exposure to each stimulus, its experience-weight increases, resulting in a reluctance to update beliefs about this stimulus. This feature makes the EWA model particularly suitable for modelling reversal learning impairment, effectively embodying a learning rate that reduces over time thus rendering behavior less flexible. The EWA model is described by the following equations:

$$\begin{aligned} n_{c,t+1} &= n_{c,t} \times \rho + 1 \\ V_{c,t+1} &= (V_{c,t} \times \varphi \times n_{c,t} + \lambda_t) / n_{c,t+1} \\ V_{\sim c,t+1} &= V_{\sim c,t} \end{aligned} \quad (1)$$

where $n_{c,t}$ is the experience-weight of choice c on trial t , which is updated on every trial, using the experience decay factor ρ . The expected value of choice c on trial t , $V_{c,t}$, is updated by integrating the feedback, $\lambda_t \in \{-1, 1\}$, the decay factor for previous payoffs (inverse learning rate), φ , and the experience-weight $n_{c,t}$. Initially, the effective learning rate for each choice is high ($ELR = 1/(1 + \varphi)$), by increasing the experience-weight to its asymptote point ($n_{\infty} = 1/(1 - \rho)$), the learning rate will decrease and converge to $ELR_{c,\infty} = 1/(1 \times \varphi \times n_{c,\infty}) = (1 - \rho)/(1 - \rho + \varphi)$. Therefore, by experiencing a choice, the experience-weight increases, resulting in a reluctance to update the stimulus value based on new outcomes. The value of unchosen options $V_{\sim c,t}$, remains unchanged.

In M2, M1 is augmented with a forgetting rate. The current version of this task has three choice options. Therefore, in comparison with the two-option task, it is more likely that an option remains unchosen on consecutive trials. Thus, the value of an unchosen option may be ‘forgotten’. In this EWA+F model, the value of unchosen options is ‘forgotten’ by pulling these to their initial value (Ito and Doya 2009):

$$V_{\sim c,t+1} = (1 - \alpha_f) V_{\sim c,t} \quad (2)$$

here, α_f is the forgetting rate. For $\alpha_f = 0$, the model is equivalent to the base EWA model (Eq. 1) and for more positive values, the value of the unselected option will converge to the initial value faster.

In the EWA models, the learning rate can only decrease over time (or remain constant). However, it would be adaptive to decrease learning rates in periods of stability and increase learning rates in periods of change. Indeed previous studies have been shown that people are able to adjust their learning rate according to the volatility of the environment (Behrens et al. 2007). It is unclear, however, whether people adjust their learning rate when there is only a single reversal, or whether this takes multiple reversals to ‘meta-learn’ that changes take place. Furthermore, even if people do adjust their learning rate, it is unclear if we can reliably quantify this with only a single reversal. These are, however, empirical questions, and thus to assess such adaptive changing of the learning rate, M3 and M4 comprised models (Li et al. 2011; Piray et al. 2019) where the learning rate is a function of the absolute value of previous

prediction error (surprise signal). Following reversal, continued choice of the initially rewarded stimulus will lead to a series of prediction errors, thus increasing the learning rate and allowing for faster reversal. In this hybrid model, values are updated as follows:

$$\begin{aligned}
\delta_t &= o_t - V_{c,t} \\
\alpha_t &= \kappa A_t \\
V_{c,t+1} &= V_{c,t} + \alpha_t \delta_t \\
V_{\sim c,t+1} &= V_{\sim c,t} \\
A_{t+1} &= \eta |\delta_t| + (1 - \eta) A_t
\end{aligned} \tag{3}$$

where κ is scale of learning rate and η determines the step size for updating associability of the cue. On each trial, the learning rate α_t , depends on associability A_t , which itself is updated based on absolute prediction error from the past trials, but not the current one. Therefore, δ_t is not double counted in the value update, so this makes δ_t and A_t relatively uncorrelated. Note that, the value of unchosen options $V_{\sim c,t}$, remains unchanged.

Finally, in M4, model M3 was augmented with a forgetting rate, where unchosen options are updated using Eq. 2.

For all models, to select an action based on the computed values, a soft-max function was employed to calculate the probability of each choice.

$$P(c_t = i) = \frac{\exp(\beta V_{c=i,t})}{\sum_j \exp(\beta V_{c=j,t})} \tag{4}$$

here, β is the inverse temperature parameter. The $j \in \{1,2,3\}$ contains the possible actions.

We first fitted and compared these 4 ‘base’ models across both drug and placebo sessions, to establish the best model independent of drug (cf. model fitting and comparison, below). We then extended the winning model to understand what mechanism drove the behavioural difference between placebo and methylphenidate sessions. For this, we built a collection of models where we allowed each parameter in turn to be estimated separately for the methylphenidate and placebo sessions (cf. Swart et al. 2017).

Model Fitting & Comparison

All models were fitted to the trial-by-trial choices and feedback of each individual participant using Hierarchical Bayesian Inference (HBI) (Piray et al. 2019). The HBI procedure employs a full hierarchical Bayesian approach for concurrent parameter estimation and random effect model comparison. This method uses variational Bayes (Jordan et al. 1998), an extended version of expectation-maximization (Dempster et al. 1977), for estimating individual and group-level parameters using an iterative algorithm. The random effects approach assumes that different models might be responsible for generating data for different participants. Therefore, participants have different influences on updating group-level parameters (mean and variance). In other words, better-fitted participants have more weight (role) in updating the group-level parameters based on a so-called responsibility measure, quantifying the probability that each model is responsible for generating data for a particular participant.

For model comparison, the best model was determined using random effects model comparison (Rigoux et al. 2014; Stephan et al. 2009), which uses a Laplace approximation (Daw 2011; Kass and Raftery 1995) of model evidence for each individual participant in order to compute the group evidence. This metric quantifies how well each model fits to the data, penalized for model complexity.

The unique characteristic of the HBI method is that it simultaneously solves two dependent problems, parameter estimation and model comparison, using a fully Bayesian approach. Additionally, the random effects approach results in a more robust model comparison and model selection, less driven by outliers than fixed-effects methods. The winning model was selected based on the protected exceedance probability (Rigoux et al. 2014) and model frequency. For parameter estimation, a wide Gaussian prior was assumed for all parameters, zero mean and a variance of 10. Then, according to theoretical constraints of parameters, $\rho, \varphi, \alpha_f, \kappa, \eta \in [0,1]$ and $\beta \in [0, +\infty)$, we apply sigmoid and exponential transformations, respectively.

Model validation

Model comparison evaluates whether a winning model is better than other models using an estimation of model evidence, which evaluates goodness of fit relative to model complexity for the models. The winning model should have the ability to regenerate the raw data besides minimizing the objective function. Therefore, in addition to model fitting we also performed model simulation for the winning model to evaluate the model ability to regenerate key features of the data. We generated simulation data using the winning model, the task paradigm, and the optimal fitted parameters for each participant. Using each participant's parameters, 100 artificial agents are simulated and then averaged to represent each individual participant's behaviour. Trial-by-trial simulated data were compared to the raw data.

Covariate analyses

Listening Span Test

The listening span test (Daneman and Carpenter 2004; Salthouse and Babcock 1991) was administered at the beginning of the second test session to obtain an estimate of participants' working memory capacity, as a putative proxy of baseline dopamine synthesis capacity. During this test, participants listened to pre-recorded sentences and were given two tasks: They answered simple written multiple-choice questions about the content while remembering the last word of each sentence for later recall. The number of sentences on each trial (i.e. the span) increased up to 7 over the course of the task. Three series of each span were conducted. The trial was coded as successful if the answers to the multiple choice questions were correct and if all last words were remembered and reported in the correct order. Based on participants' performance a listening span was calculated ranging from 0 to a maximum of 7. The highest level for which two out of the three series were correctly remembered comprised the *basic span*. Half a point was added if one series of the following span was correctly completed, resulting in the measure of *total span*. Total span has been shown to correlate positively with dopamine synthesis capacity (Cools et al. 2008; Landau et al. 2009). Both studies have reported large effect sizes for the correlations between listening span scores and dopamine synthesis capacity. In addition, listening span scores have been

shown to predict dopaminergic drug effects (Kimberg et al. 1997; Frank et al. 2006; Cools and D’Esposito 2011; Kimberg and D’Esposito 2003; Van der Schaaf et al. 2014).

Table 1. Demographic and background characteristics of participants included in the analysis.

N=102	Characteristic	Measure	mean (st.d.)	min-max	range*
Demographics	Age	Years	21.5 (2.3)	18-28	-
	Gender	Men/women (number)	51/51	-	-
Experimental information	Order	Placebo first / MPH first (number)	52/50	-	-
	Mean delay MPH to task start	Minutes	186.1 (7.9)	-	-
Neuropsychological assessment	Verbal intelligence	NLV	93.5 (7.7)	75 - 114	55 - 145
	Working memory capacity	Listening span: total span Digit span**	4.8 (1.0)	2.5 - 7	0 – 7
		Forward	16.7(3.6)	10 - 26	0 - 28
		Backward	14.4(3.1)	8 - 23	0 – 28
Self-report Questionnaires	Impulsivity	BIS-11: total score	61.8 (8.5)	43 - 93	30 - 120
	Need for Cognition	NCS	63.4 (10.5)	38 - 82	18 - 90
	Depressive symptoms	BDI	3.5 (3.8)	0 - 21	0 - 63
	Behavioral activation	BAS: total score	23.3 (4.0)	15 - 34	13 - 52
	Behavioral inhibition	BIS	16.3 (3.5)	7 - 23	7 - 28
	Anxiety symptoms	STAI	32.5 (6.9)	23 - 55	20 - 80
	Social support	MDSPSS: total	70.4 (9.5)	43 - 84	12 - 84
	Social status	BSMSS: total	47.9 (12.6)	14.5- 66	8 - 66
	Social dominance	SADQ: social	4.1 (0.8)	2.1 - 5.9	1 - 7
	Aggressive dominance	SADQ: aggressive	2.6 (0.6)	1.3 - 4.6	1 - 7

Demographic and background characteristics of participants included in the analysis. Questionnaires included the Beck Depression Inventory (BDI; Beck et al., 1996), Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS; Carver & White, 1994), Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995), Need for Cognition Scale (BCS; Cacioppo et al., 1984), Spielberger Trait Anxiety Inventory (STAI; Spielberger et al., 1983), Multidimensional Scale of Perceived Social Support (MDSPSS; Zimet, Dahlem, Zimet, & Farley, 1988), Social and Aggressive Dominance Questionnaire (SADQ; Kalma, Visser, & Peeters, 1993) and Barratt Simplified Measure of Social Status (BSMSS; Barratt, 2006). Reported scores are comparable with observations in healthy populations in earlier reports. Listening span, e.g. Salthouse & Babcock, 1991; Digit span, e.g. van der Schaaf et al., 2014: FW mean = 8.5; BW mean = 7.9; BIS-II, e.g. Buckholtz et al. 2010: mean = 59.5, NCS, e.g. Westbrook et al., 2013:

mean = 64.5; BDI, e.g. Schulte-Van Maaren et al. 2013: mean = 3.7; BIS/BAS, e.g. Franken et al. 2005: mean BIS = 13.8, mean BAS = 24.5; STAI, e.g. De Weerd et al. 2001: mean $\approx$ 34; MDSPSS, e.g. Canty-Mitchell & Zimet, 2000: mean = 5.5; BSMSS, e.g. Cook et al., 2014: mean = 49.0, 42.6; SADQ, e.g. Cook et al., 2014: social mean = 4.0, 3.9; aggressive mean = 2.9, 2.7. The verbal IQ estimate (NLV) seems low in this sample (relative to e.g. van der Schaaf et al., 2014: mean = 101). However, we tested a student population and we expect this value to be low due to the outdated character of the test (1991), not accommodating changes in language use, particularly integration of English words in the Dutch language.

*Note: range reflects the possible range of scores on the questionnaires, whereas min - max and mean (st.d.) reflect the participant data.

** scores represent an average across two testing days

Trait impulsivity

A series of questionnaires was completed by participants at home between the two test sessions. The trait impulsivity questionnaire was key to our research question and will be described in more detail below. The other questionnaire data were acquired for exploratory purposes, not pursued here, and are presented in Table 1. Trait impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-11; Patton et al. 1995). The BIS-11 is a self-report questionnaire, consisting of 30 statements tapping in common (non)impulsive behaviours and preferences, that participants rate on a 4-point Likert scale ("never" to "almost always"). Scores have been found to be associated with dopamine D2/D3 receptor availability in the midbrain, and enhanced dopamine release in the striatum (Buckholtz et al. 2010; Kim et al. 2014; Lee et al. 2009; Reeves et al. 2012) and has been shown to predict effects of methylphenidate on learning (Clatworthy et al. 2009). This measure serves as a second putative proxy of baseline dopamine function for predicting effects of methylphenidate. The effect sizes for the correlations between Barratt total scores and D2/D3 receptor availability ranged from small (Lee et al. 2009) to large (Buckholtz et al. 2010). Participants completed the questionnaire at home between test days. Three participants did not complete one (n=2) or two (n=1) items of the questionnaire. For these items, we used the mean answer across all participants.

Mood and Medical Symptom Rating

Mood ratings, heart rate and blood pressure were monitored for safety reasons three times during each test day, i) before capsule intake, ii) upon start task battery, and iii) upon completion of the task battery. The mood ratings consisted of the Positive and Negative Affect Scale (PANAS; Watson et al. 1988) and the Bond and Lader Visual Analogues Scales (calmness, contentedness, alertness; Bond and Lader, 1974), as well as a medical Visual Analogues Scale.

We assessed whether methylphenidate affected mood and medical symptoms. For this control analysis, we performed a repeated measures MANOVA using Pillai's trace with the within subject factors Time (prior to drug intake; prior to the first task; at the end of testing, see *Figure 1A*) and Drug (methylphenidate/placebo), and dependent variables Positive Affect, Negative Affect, Calmness, Contentedness, Alertness, and Medical Symptoms, with a follow-up MANOVA of baseline (T1) effects only, with factor Drug and the same dependent variables. Significant effects were further explored with Bonferroni corrected repeated measures ANOVA comparing pre (T1) vs post (T2, T3) intake (Helmert contrast), where $\alpha = .05/6 \approx .008$. Greenhouse-Geisser correction was applied when the assumption of sphericity was not met. Finally, we assessed whether Listening Span and Impulsivity interacted with the effects of methylphenidate on the self-report rating, by including these covariates in the main MANOVA.

Methylphenidate affected self-report ratings (Time x Drug: $V = .38$, $F(12,89) = 4.6$, $p < .001$), in the absence of baseline (T1) differences between the methylphenidate and placebo groups (T1 only, Drug: $V = .06$, $F(6,95) = 1.0$, $p = .5$). After capsule intake, relative to placebo methylphenidate increased Positive Affect ($F(1,100) = 19.9$, $p < .001$), Alertness ($F(1,100) = 16.8$, $p < .001$), and Medical Symptoms ($F(1,100) = 9.9$, $p = .002$), decreased Calmness ($F(1,100) = 7.9$, $p = .006$), and did not significantly affect Contentedness ($F(1,100) = 1.4$, $p = .23$) and Negative Affect ($F(1,100) = 0.4$, $p = .5$). The effects of methylphenidate on the self-report ratings did not significantly interact with Listening Span (Drug x Time x WMspan: $V = 0.1$, $F(12,87) = 0.8$, $p = .7$) and Impulsivity (Drug x Time x BIS: $V = 0.2$, $F(12,87) = 1.8$, $p = .063$), which suggests that the methylphenidate-induced changes in mood and medical symptoms were orthogonal to the Listening Span dependent methylphenidate effects we observed on the task of interest here.

RESULTS

Data quality Assessment

All 102 healthy participants completed the probabilistic reversal learning task in two sessions, and were included in the analysis. No participants chose the same response option throughout. Participants made very few responses with RT <200 ms (mean (st.d.) 0.2 (0.6)% of trials, range 0 - 4%), these trials were excluded for the basic analyses. For computational modelling, analyses were repeated with and without these trials.

Behavioural analyses

Accuracy

Participants successfully learned the three-option PRL task. People were more likely to select the Rewarded rather than the Punished stimulus ($F(1,99) = 564.1$, $p < .001$; *Figure 1C*). However, participants showed some degree of perseveration, as choice accuracy was lower during the reversal phase (Valence x Phase, $F(1,99) = 19.7$, $p < .001$, c.f. *Figure 1D*). Participants were both more likely to select the Punished option in the reversal phase, i.e. they stuck to the previously rewarded option (a simple effect of Phase for the Punished stimulus: $F(1,99) = 38.1$, $p < .0001$), and were less likely to select the Rewarded stimulus in the reversal phase, i.e. they were reluctant to select the previously Punished stimulus (a simple effect of Phase for the Rewarded stimulus: $F(1,99) = 9.8$, $p = .002$). Note that these effects could be estimated separately because the inclusion of the neutral response option renders them (relatively) independent.

Methylphenidate did not consistently affect either overall learning (Valence x Drug, $F(1,99) = 3.3$, $p = .074$), nor differential learning during acquisition and reversal (Valence x Phase x Drug: $F(1,99) = 0.6$, $p = .43$). However, methylphenidate affected performance as a function of WM span (Valence x Phase x Drug x WM span: $F(1,99) = 7.1$, $p = .009$, *Figure 2C*). To understand the nature of this interaction we broke it down into simple effects for each of the factors *Table 2*. Breaking down by Phase provided the most parsimonious explanation of the observed interaction. Surprisingly, this uncovered an effect of methylphenidate during the acquisition, but not during the reversal phase of the task. During the acquisition phase, people with high working memory improved under methylphenidate, while people with low working

memory performed more poorly (*Figure 2B*). In contrast, during reversal there was no interaction of performance with drug and working memory span.

Finally, there were some weak (trend) lower level interaction effects that were however qualified by the key higher-order interaction described above (Valence x Drug: $F(1,99)=3.3$, $p=.074$; Valence x Drug x WM span: $F(1,99)=3.6$, $p=0.06$; Phase x Drug x WM span: $F(1,99)=5.4$, $p=0.022$). There was no significant effect of BIS on performance, nor in interaction with methylphenidate (Valence x Phase x Drug x BIS: $F(1,99)=0.07$, $p=0.8$, all other $p>0.1$).

Table 2. Post hoc simple interaction analyses of WM span mediated effect of methylphenidate.

Valence x Phase x Drug x WM span	$F(1,99)=7.1$, $p=.009$
Valence x Drug x WM span	
<i>Acquisition</i>	$F(1,99)=9.8$, $p = .002^{**}$
<i>Reversal</i>	$F(1,99)=0.1$, $p = .75$
Phase x Drug x WM span	
<i>Rewarded</i>	$F(1,99)=7.6$, $p = .007^{**}$
<i>Punished</i>	$F(1,99)=3.7$, $p = .057$
Phase x Valence x WM span	
<i>Methylphenidate</i>	$F(1,99)=4.5$, $p=.037^{*}$
<i>Placebo</i>	$F(1,99)=1.3$, $p=.25$

To control for potential confounding factors, we repeated this ANOVA by including the confound variables gender and test order (between subject factors) and age (covariate). Including these confound variables did not alter the significance of the observed effects although there was an effect of age (but this did not interact with the effect of interest, for details see the supplemental results & discussion 1).

Feedback sensitivity

We also evaluated immediate effects of feedback, by assessing the degree to which an outcome affected subsequent choice. Overall, participants were more likely than chance to repeat a choice on the subsequent trial (Main effect of $p(\text{Stay})$: $F(1,99) = 541.3$; $p<.001$; *Figure 1E*). However, they were less likely to repeat their choice following a Loss than following a Win (Outcome: $F(1,99)=302.9$, $p<.0001$), indicating subsequent choice was modulated by feedback. This effect was weaker during the reversal phase (Outcome x Phase: $F(1,99)=21.6$, $p<.0001$), putatively in line with slower learning during reversal. However, there was no significant effect of methylphenidate on either the overall tendency to stay (Drug: $F(1,99)=2.2$, $p=.13$), nor its modulation by Outcome (Outcome x Drug: $F(1,99)=0.4$, $p=.5$), nor did this change over time (Outcome x Phase x Drug: $F(1,99)=2.4$, $p=.12$).

For completeness, there was a trend towards an interaction of Drug x WM on the tendency to stick to a particular choice, regardless of feedback (Drug x WM: $F(1,99)=3.04$, $p=.084$). There were no further significant interactions of the effects of methylphenidate predicted by BIS or WM (all $p>0.3$).

A - No main effect of MPH on average choice

B - Average trial-by-trial Choice

C - MPH effects predicted by WM span

Figure 2. Effects of Methylphenidate on reversal learning task performance. **A.** No significant main effect of methylphenidate on average probability of stimulus selection. Distribution of difference of stimulus selection probability between two sessions (MPH-placebo) for acquisition and reversal phase demonstrated in dark and light blue, respectively. Methylphenidate did not consistently affect either overall learning or differential learning during acquisition and reversal. **B.** Trial-by-trial averaged probability of selection of each stimulus (median split based on WM span). Left panel: high WM group ($n=48$), probability of ‘Rewarded’ stimulus selection increased under methylphenidate (dash line) in comparison to placebo (solid line) during the acquisition phase. Right panel: low WM group ($n=54$), probability of ‘Rewarded’ stimulus selection decreased under methylphenidate in comparison to Placebo during the acquisition phase. A sliding window with 5-trial width is used for smoothing. **C.** Methylphenidate effects predicted by WM span. Methylphenidate increased the accuracy of selecting ‘Rewarded’ option vs ‘Punished’ option in acquisition phase more than reversal phase for high WM span participants, yet decreased it for low WM span participants ($r=.26$, $p=.009$). By splitting up the MPH effect by phase factor, during the acquisition, middle panel, participants with high WM improved under methylphenidate ($r=.30$, $p=.002$), but during the reversal, right panel, there is no significant interaction.

Model Comparison

We compared our previously established EWA model to an extended version that included a forgetting factor, following from the extension of stimulus space (3-option design) along with the hybrid models (M3 and M4) that allowed for adaptive, prediction-error-based changes in learning rate. Model comparison showed convincing evidence in favor of the EWA+F model M2 (protected exceedance probability: 0.91, *Figure 3A*). See *Table 3* for parameter estimates for all four base models.

A - Model comparison on base models

B - Trial-by-trial simulated choice

C - Simulated average choice probability

Figure 3. Model fitting and simulation result for PRL task modelling. **A.** Model comparison on base models. Model frequency and protected exceedance probability indicate that the EWA+F model (EWA with forgetting rate for unchosen options) provides the best description of the data (PEP = 0.91). **B.** Trial-by-Trial simulated choice. Model simulations of the winning base model verify that the EWA+F model captures the behavioural data (grey lines indicate average raw data). **C.** Simulated average choice probability. Distribution of stimulus selection probability for acquisition and reversal phase demonstrated in dark and light blue, respectively (compare with figure 1D). The simulated data for EWA+F model qualitatively and quantitatively replicate the participants' behaviour and regenerate key features of the data.

Table 3. Subject-level optimal parameter estimates for base models

Model	Parameter	Prior ⁺	Constraint	Median	Range (25%-75%)	pxp _i	P(m _i data, m)
M1: EWA						0.01	0.22
	φ	$N(0,10)$	$0 \leq \varphi \leq 1$	0.56	0.25 – 0.71		
	ρ	$N(0,10)$	$0 \leq \rho \leq 1$	0.51	0.21 – 0.69		
	β	$N(0,10)$	$0 \leq \beta \leq +\infty$	3.16	2.46 – 4.53		
M2: EWA+F						0.91	0.40
	φ	$N(0,10)$	$0 \leq \varphi \leq 1$	0.77	0.29 – 0.87		
	ρ	$N(0,10)$	$0 \leq \rho \leq 1$	0.63	0.27 – 0.83		
	β	$N(0,10)$	$0 \leq \beta \leq +\infty$	4.23	3.11 – 7.88		
	α_f	$N(0,10)$	$0 \leq \alpha_f \leq 1$	0.35	0.02 – 0.68		
M3: Hybrid						0.0	0.10
	κ	$N(0,10)$	$0 \leq \kappa \leq 1$	0.57	0.42 – 0.76		
	η	$N(0,10)$	$0 \leq \eta \leq 1$	0.23	0.02 – 0.60		
	β	$N(0,10)$	$0 \leq \beta \leq +\infty$	3.35	2.09 – 4.85		
M4: Hybrid+F						0.08	0.28
	κ	$N(0,10)$	$0 \leq \kappa \leq 1$	0.35	0.18 – 0.69		
	η	$N(0,10)$	$0 \leq \eta \leq 1$	0.22	0.05 – 0.71		
	β	$N(0,10)$	$0 \leq \beta \leq +\infty$	5.73	3.06 – 10.03		
	α_f	$N(0,10)$	$0 \leq \alpha_f \leq 1$	0.29	0.02 – 0.68		
⁺ A weakly informative Gaussian prior was used for all parameters ($x \sim N(\mu, \sigma^2)$) where μ is mean value and σ^2 is variance of Gaussian distribution). According to theoretical constraints of parameters, sigmoid or exponential transformations are applied.							

To capture the effects of methylphenidate, we allowed each of the 4 parameters of this winning model to be affected by methylphenidate in turn, by fitting that parameter separately for methylphenidate and placebo sessions. We then compared all 4 ‘drug’ models plus the ‘baseline’ model without an effect of methylphenidate. Model comparison showed that the winning model allows methylphenidate to affect the inverse learning rate parameter φ (protected exceedance probability: 0.98, see *Figure 4B*). Parameter estimates for the methylphenidate models and model comparison statistics are reported in *Table 4*.

Posterior predictive checks

Model simulation is essential to evaluate the model’s ability to regenerate key features of the data. In order to examine the reproducibility of the winning model, we generated data using the winning model. Our simulated data qualitatively and quantitatively replicate the participants’ behaviour (*Figure 3B-C* and *Figure 4C-D*). Again, in the simulated data, there is a significant interaction of Valence x Phase x Drug x WM span ($F(1,99)=5.1$, $p=.027$) (*Figure 4D*). Furthermore, breaking down this interaction into simple effects by phase, our observations from raw data were replicated. Methylphenidate improved initial learning in high-WM span participants, while reducing performance in low-WM span participants ($F(1,99)=5.1$, $p=.027$). Again, there was no significant Valence x Drug x WM span interaction during the reversal phase ($F(1,99)=1.7$, $p=.3$).

Figure 4. Modelling the effects of Methylphenidate. **A.** Simulated choice. Simulated data replicated observed behaviour for no main effect of methylphenidate (see Figure 2A). **B.** Model comparison on methylphenidate models. Model frequency and protected exceedance probability (PEP = 0.98) indicate that the EWA+F that allows for differential learning rates under methylphenidate and placebo best captures the data. Model validation: C-F. **C.** Simulated trial-by-trial behaviour. Simulated data replicate observed behaviour for high WM and low WM participants (see Figure 2B). **D.** Choice simulation. The simulated data using winning model regenerate quantitative characteristics of data, particularly a positive effect of methylphenidate on performance for high WM participants (see Figure 2C). **E.** Methylphenidate changes inverse learning rate as a function of working memory span. The difference in inverse learning rates under methylphenidate vs placebo ($\Delta\phi$) covaries with WM span ($r=0.2$; $p=0.043$). Methylphenidate increases ϕ in high WM participants, where decreases it in low WM participants. **F.** Methylphenidate-induced effect on raw performance scores. The methylphenidate-induced change in inverse learning rate ($\Delta\phi$) is correlated with methylphenidate-induced change in raw performance ($r=0.33$; $p<0.001$).

Table 4. Subject-level optimal parameter estimates for methylphenidate effect models

Model	Parameter	Prior ⁺	Constraint	Median	Range (25%-75%)	pxp _i	P(m _i data, m)
M2: Baseline						0.02	0.25
	φ	$N(0,10)$	$0 \leq \varphi \leq 1$	0.77	0.29 – 0.87		
	ρ	$N(0,10)$	$0 \leq \rho \leq 1$	0.63	0.27 – 0.83		
	β	$N(0,10)$	$0 \leq \beta \leq +\infty$	4.23	3.11 – 7.88		
	α_f	$N(0,10)$	$0 \leq \alpha_f \leq 1$	0.35	0.02 – 0.68		
M2a: Δ_φ						0.98	0.42
	$\varphi_{Placebo}$	$N(0,10)$	$0 \leq \varphi_{Placebo} \leq 1$	0.70	0.26 – 0.86		
	φ_{MPH}	$N(0,10)$	$0 \leq \varphi_{MPH} \leq 1$	0.70	0.33 – 0.84		
	ρ	$N(0,10)$	$0 \leq \rho \leq 1$	0.56	0.21 – 0.79		
	β	$N(0,10)$	$0 \leq \beta \leq +\infty$	4.46	3.13 – 7.94		
	α_f	$N(0,10)$	$0 \leq \alpha_f \leq 1$	0.22	0.01 – 0.62		
M2b: Δ_ρ						0	0.13
	φ	$N(0,10)$	$0 \leq \varphi \leq 1$	0.73	0.30 – 0.86		
	$\rho_{Placebo}$	$N(0,10)$	$0 \leq \rho_{Placebo} \leq 1$	0.56	0.23 – 0.82		
	ρ_{MPH}	$N(0,10)$	$0 \leq \rho_{MPH} \leq 1$	0.52	0.23 – 0.78		
	β	$N(0,10)$	$0 \leq \beta \leq +\infty$	4.79	3.34 – 7.83		
	α_f	$N(0,10)$	$0 \leq \alpha_f \leq 1$	0.28	0.02 – 0.65		
M2c: Δ_β						0	0.08
	φ	$N(0,10)$	$0 \leq \varphi \leq 1$	0.68	0.28 – 0.85		
	ρ	$N(0,10)$	$0 \leq \rho \leq 1$	0.55	0.20 – 0.83		
	$\beta_{Placebo}$	$N(0,10)$	$0 \leq \beta_{Placebo} \leq +\infty$	4.21	2.76 – 8.54		
	β_{MPH}	$N(0,10)$	$0 \leq \beta_{MPH} \leq +\infty$	4.32	2.90 – 9.37		
	α_f	$N(0,10)$	$0 \leq \alpha_f \leq 1$	0.25	0.02 – 0.64		
M2d: Δ_{α_f}						0	0.12
	φ	$N(0,10)$	$0 \leq \varphi \leq 1$	0.66	0.31 – 0.86		
	ρ	$N(0,10)$	$0 \leq \rho \leq 1$	0.61	0.25 – 0.82		
	β	$N(0,10)$	$0 \leq \beta \leq +\infty$	4.80	3.18 – 7.43		
	$\alpha_f Placebo$	$N(0,10)$	$0 \leq \alpha_f Placebo \leq 1$	0.26	0.02 – 0.60		
	$\alpha_f MPH$	$N(0,10)$	$0 \leq \alpha_f MPH \leq 1$	0.21	0.02 – 0.49		

⁺ A weakly informative Gaussian prior was used for all parameters ($x \sim N(\mu, \sigma^2)$ where μ is mean value and σ^2 is variance of Gaussian distribution). According to theoretical constraints of parameters, sigmoid or exponential transformations are applied.

Parameter inference

There was clear evidence for model M2, which allowed for a different value for the inverse learning rate φ on vs. off methylphenidate. Despite this evidence, there was no significant difference between $\varphi_{Placebo}$ and φ_{MPH} when assessed across all individuals ($t = -0.4$, $p = 0.68$). This indicates strong evidence for a change in φ following drug intake, but the direction of this change was variable over participants. Indeed, mirroring the raw behavioural results, the difference between $\varphi_{Placebo}$ and φ_{MPH} correlated with WM span ($r = 0.20$, $p = .043$, Figure 4E). There was a strong correlation between methylphenidate-induced changes in inverse learning rate (Δ_φ) and the methylphenidate-induced change in raw performance metrics ($r = 0.32$, $p < .001$, Figure 4F). Thus, methylphenidate administration increased performance in high working memory participants, which was captured by an increase in the inverse learning rate φ , thus effectively a decrease in learning rate. In contrast, methylphenidate

administration decreased performance in low working memory participants, which was captured by a decrease in inverse learning rate φ .

Optimal learning rate analysis

Compared with previous studies in which tasks were employed with two response options, we observed that performance in the acquisition phase was substantially worse, while performance during the reversal phase was much better in our current 3-option version (cf. den Ouden et al. 2013). Concomitant with this, values of φ were much higher, i.e. an effective decrease in learning rate, in the current dataset than in our previous dataset. We therefore performed a supplemental analysis to compare the optimal learning rates across the two different versions of the task. In short, the 3-option version of the task had a lower optimal learning rate. Accordingly, the decrease in learning rate in high WM span participants under methylphenidate was adaptive: the effective learning rates moved closer to the optimal learning rate. For details, see supplemental results & discussion 2.

DISCUSSION

This study aimed to uncover the causal role of dopamine in perseverative behaviour during probabilistic reversal learning. To this end, a large sample of participants ($n=102$) performed a novel 3-choice PRL task both on and off catecholamine transporter blocker methylphenidate. Contrary to predictions, methylphenidate did not consistently affect perseverative behaviour in this novel task, as indexed by an absence of change in reversal performance. In contrast, methylphenidate altered performance in the acquisition phase, in a manner that depended on individual variability in working memory span. Specifically, methylphenidate reduced effective learning rates in participants with high working memory span, thereby improving initial learning. Conversely, methylphenidate increased effective learning rates in individuals with low working memory span.

Methylphenidate effects on value-learning versus perseveration

We set out in this study to assess the computational mechanism by which catecholamine blockade affects reversal performance. Specifically, we asked whether reversal deficits were due to a failure to learn to approach a previously punished stimulus or to ‘let go’ of a previously rewarded stimulus. Perhaps a surprising finding in the current study is that acute catecholamine reuptake blockade did not affect reversal performance and perseveration at all. This is particularly surprising given the considerable literature concerning the role of dopamine in habitual actions (Balleine and O’Doherty 2010; Daw et al. 2005; Everitt and Robbins 2005) and perseverative behaviour (Cools et al. 2001; Rutledge et al. 2009), particularly direct findings of genetic variability in the *DAT1* genotype (den Ouden et al. 2013) and methylphenidate-induced reversal impairments (Clatworthy et al. 2009). While it is possible that this observed discrepancy between the previous literature and current study reflects a true non-replication in this large sample ($N=102$, vs. most previous studies $N=20-40$), a perhaps more likely possibility is that, by introducing a neutral choice option, we have significantly altered the nature of the paradigm.

Indeed, as presented in the supplemental analyses, across participants we observed that compared to the previously used 2-choice PRL paradigms, the learning rate was significantly lower. This reduction in effective learning rate provides an important clue as to why the observed effects in the current study are particularly obvious in the acquisition phase. By

including the 50/50 choice option, the task was rendered much more difficult as optimal performance now required dissociation of two choice options (50/50 vs 75/25) that were much closer in terms of feedback than the previous (70/30 vs 30/70) dissociation that had to be learnt. To be able to make this dissociation, one needs to integrate information over a longer window, which is exactly what a reduced learning reflects. Indeed, this adjustment is adaptive, as optimal learning rates in the current paradigm are much lower than for the previous version of the task. In contrast, performance during the reversal phase was much more robust in the current paradigm.

This increased task difficulty may have had the unanticipated effect that this (difficult) initial learning was less robust across participants, and became more sensitive to (e.g. drug) manipulations. We propose that dopamine affects both initial value learning, likely through ventral striatal prediction-error like RL mechanisms that affect learning rate, but also affects longer term ‘stamping in’ of responses and habit formation, through dorsal-striatal habit systems. Discrepancies in findings across studies, then, might reflect the relative sensitivity of various tasks tapping into these mechanisms. Thus, the current paradigm increased difficulty of initial learning, but was also associated with less vulnerable reversal performance, while the reverse may be true for the 2-option task. It is unclear why performance during the reversal phase was so much better than in the 2-option task – perhaps the task structure was more obvious to participants. Regardless, the absence of methylphenidate effects on reversal performance therefore unfortunately did not allow us to further disentangle putative dopaminergic mechanisms of reward-based perseveration versus a failure to overcome learned avoidance.

Mechanisms of baseline-dependent effects of methylphenidate

The finding that effects of methylphenidate on behaviour vary as a function of working memory capacity was consistent with our preregistered hypothesis (trial register NTR4653, <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4653>). We posit two possible explanations for this effect. First, working memory span has been shown to correlate with striatal dopamine synthesis capacity (Cools et al. 2008; Landau et al. 2009). Given that methylphenidate acts by blocking the dopamine (and noradrenaline) transporter, it is likely that the effect of methylphenidate on catecholamine-dependent function is a function of dopamine synthesis capacity and subsequent release. While under placebo conditions, release and reuptake are in balance in both high and low synthesis capacity subjects, administration of methylphenidate could disturb this balance differentially. Specifically, if individuals with higher working memory capacity have higher release of dopamine (Cools et al. 2008; Landau et al. 2009), then methylphenidate might increase tonic levels of dopamine, paradoxically leading to reduced sensitivity to individual bursts and thus a reduced learning rate. In contrast, low working memory participants with low synthesis capacity may have very sensitive post-synaptic dopamine function, and blockade of transporters may increase the duration of post-synaptic impact of dopamine bursts, thereby effectively increasing the learning rate. A recent dopamine PET study indeed demonstrated disproportionate sensitivity of participants with low dopamine synthesis capacity to MPH-related increases in reward impact on choice (Westbrook et al. 2019).

Alternatively, the interaction between methylphenidate effects on learning and baseline working memory capacity might reflect a modulation of interactions between working memory and reinforcement learning strategies (Collins et al. 2017). Specifically, Collins and

Frank have recently established that reliance on reinforcement learning mechanisms varies with working memory load (Collins and Frank 2012). With a lower number of stimuli and short delays between presentations, subjects are more likely to rely on explicit working memory strategies to make decisions, reverting to reinforcement learning mechanisms when the load on working memory is exceeded. By analogy, we hypothesize that performance in the current task varies with individual differences in the relative weight on working memory and reinforcement learning strategies, which might well correspond with variation in working memory capacity. Moreover, methylphenidate may act on striatal levels of dopamine, as suggested above, but may also affect frontal functioning, through blockade of noradrenaline transporters in the frontal cortex (Arnsten and Dudley 2005; Berridge et al. 2006; Berridge and Devilbiss 2011; Kodama et al. 2017; Volkow et al. 2001; Volkow et al. 2012). The impact of putative direct frontal modulation on working memory functioning may differ between individuals with high versus low baseline working memory capacity, and thus differentially affect the balance between WM and RL strategies.

A final speculation is that methylphenidate plays a role via its action on either dopamine or noradrenaline transmission through optimising the adaptation of the learning rate depending on the volatility of the environment, i.e. 'meta-learning' (Muller et al. 2019; Nassar et al. 2010). This final hypothesis concurs with the conclusion from another experiment, conducted within the context of this same larger methylphenidate study, in which we employed a task explicitly designed to assess effects on learning as a function of the volatility of outcome contingencies (cf. *Figure 3*; Cook et al. 2019). Specifically that experiment revealed that methylphenidate lowered the learning rate in stable versus volatile phases of a learning task. In the current experiment, this learning rate decrease in high capacity participants was associated with an increase in performance during the acquisition phase, strengthening the inference that this decrease in learning rate was adaptive. Indeed, good performance on this probabilistic task required participants to dissociate an option rewarded on 50% of trials from an option that was rewarded on 75% of trials. Integrating information over too short a time window (i.e. a high learning rate) would have made it more difficult to correctly dissociate between these two options, reducing performance. We do note that this 'meta-learning' interpretation should be taken with caution, because the current paradigm with its single reversal was not optimised to answer this question, and the models in which we allowed the learning rate to fluctuate according to the size of the prediction errors did not perform better than the winning model in which the learning rate was only allowed to be reduced over time.

Conclusion

The present study was set up to test the specific hypothesis, derived from our previous dopamine genetic study, that administration of methylphenidate would alter probabilistic reversal learning by changing the reliance on prior reward. To test this hypothesis, a novel reversal task was employed with three choice options. Surprisingly, results revealed no effects on the reversal phase. However, an effect of methylphenidate surfaced already in the initial acquisition phase. In line with prior studies, this effect was not unidirectional across participants, but varied with individual differences in baseline working memory capacity: Methylphenidate improved performance and reduced the effective learning rate to a greater degree in participants with higher working memory capacity. We hypothesize that the increased demands for learning in this 3-option task brought to the surface an effect of methylphenidate on learning rather than on flexibility.

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Author contributions

HEMdO, RC, JCS designed the paradigm; JLC, JCS, RC, HEMdO, set up the MPH study; JCS, MIF, JLC, HEMdO collected the data; DEMG provided medical cover and assistance; MRK and HEMdO analysed the data; MRK, AHV, MNA, RC, HEMdO have discussed analyses and modeling results. MRK, RC, HEMdO wrote the manuscript; all authors edited/revised the manuscript.

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Supplemental Methods

1. Overview of exclusion criteria

- (History of) psychiatric treatment
- (History of) neurological treatment
- (History of) endocrine treatment
- (History of) autonomic failure (e.g., vasovagal reflex syncope).
- (History of) clinically significant hepatic, cardiac, obstructive respiratory, renal, cerebrovascular, metabolic or pulmonary disease
- Family history of sudden death or ventricular arrhythmia
- (History of) epilepsy
- (History of) drug dependence (opiate, LSD, (meth)amphetamine, cocaine, solvents, or barbiturate) or alcohol dependence
- Suicidality
- Abnormal hearing or (uncorrected) vision.
- Use of MAO inhibitor, anaesthetic, anti-depressant or antipsychotic drugs within the week prior to the start of the study.
- Use of psychotropic medication, or of recreational drugs over a period of 24 hours prior to each test session, and use of alcohol within the last 24 hours before each measurement.
- Regular use of corticosteroids.
- Uncontrolled hypertension, defined as diastolic blood pressure at rest > 95 mmHg or systolic blood pressure at rest > 180 mmHg
- Hypotension, defined as diastolic blood pressure < 50 mm Hg or systolic < 95 mm Hg or resting pulse rate < 45 beats/min
- Diabetes
- Family history of schizophrenia, bipolar disorder or major depressive disorder
- Irregular sleep/wake rhythm (e.g., regular nightshifts or cross timeline travel).
- Possible pregnancy or breastfeeding
- Lactose intolerance (placebo pill is a lactose product)

2. Medical symptoms rating scale

1. No headache	Strong headache
2. No muscle pain	Strong muscle pain
3. No dry mouth	Very dry mouth
4. Not dizzy	Very dizzy
5. No abdominal pain	Strong abdominal pain
6. No joint pain	Strong joint pain
7. No trouble breathing	Trouble breathing
8. No throat pain	Strong throat pain
9. No chest pain	Strong chest pain
10. No eye problems	Strong eye problems

Supplemental results & discussion

1. Control analyses

Age, gender, test order and NLV (Nederlandse Leestest voor Volwassenen – Dutch Adult Reading Test, a measure of verbal intelligence) are potential factors that may explain variance in behaviour. We therefore included these covariates (age, NLV) and factors (gender, test order) in the main analysis, primarily to assess whether inclusion of these variables affected our main findings. The interaction of Valence x Phase x Drug x WM span remained significant $F(1,94)=7.26$, $p=.008$).

We observed some interactions of age with drug, which we report here for completeness (Phase x Drug x Age: $F(1,94)=5.67$, $p=.02$; Valence x Phase x Drug x Age: $F(1,94)=4.06$, $p=.047$). However, we are reluctant to interpret these effects given that none of these interactions survive multiple comparison correction, and that the age range of our sample was narrow (mean (st.d.) = 21.5 (2.3); min-max = 18-28). Importantly, there is no significant correlation between age and WM span ($r=.08$, $p=.37$). Again for completeness, there were significant interactions of Valence x Phase x Gender ($F(1,94)=4.09$, $p=.04$) Phase x Gender x Test Order ($F(1,94)=4.17$, $p=.04$), and trends of Drug x Test Order ($F(1,94)=2.9$, $p=.092$); Drug x BIS ($F(1,94)=2.9$, $p=.092$). There were no further significant or trend effects of these nuisance variables ($F<2.2$, $p>.14$).

In light of the effect of methylphenidate on inverse learning rate ϕ as a function of working memory (WM) span, perhaps of interest to note is a near trend effect on feedback sensitivity (i.e. changes in performance driven by feedback on the previous trial), where methylphenidate tended to change the degree of staying following a win versus loss during the acquisition phase (Drug x Outcome x Phase x WM ($F(1,99)=2.4$, $p=.12$). This effect indexes the degree to which participants follow a win-stay lose-shift strategy, which is effectively a learning rate of 1. This trend effect on win-stay lose-shift may reflect the change in learning

rate that is captured by the computational model. However, because a win-stay lose-shift analysis only captures integration of information 1 trial back, this analysis is much less sensitive than our computational approach.

We also re-analysed the data excluding $RT < 200$ ms, as these are likely to reflect fast responses where stimulus values were not considered. 51 trials were excluded due to RT's under 200 ms. We confirm that our conclusions remain unchanged, as reported in *Table S1*.

Table S1. Post hoc simple interaction analyses of WM span mediated effect of methylphenidate, where trials with $RT < 200$ ms are excluded.

Accuracy x Phase x Drug x WM span	F(1,99)=7.1, p=.009
Valence x Drug x WM span	
<i>Acquisition</i>	F(1,99)=9.8, p =.002**
<i>Reversal</i>	F(1,99)=0.1, p = .75
Phase x Drug x WM span	
<i>Rewarded</i>	F(1,99)=7.6, p = .007**
<i>Punished</i>	F(1,99)=3.7, p = .059
Phase x Valence x WM span	
<i>Methylphenidate</i>	F(1,99)=4.4, p=.038*
<i>Placebo</i>	F(1,99)=1.3, p=.25

2. Effects of adding a 'neutral' choice option to reversal performance

At first sight, a puzzling aspect of our findings was that methylphenidate affected performance during acquisition, rather than reversal, in contrast to previous findings where dopamine affected perseverative behaviour (cf. den Ouden et al. 2013). Instead, we observed an effect of methylphenidate on initial acquisition of the reward contingencies. We hypothesise that through introducing an additional 'neutral' choice option (with 50/50 reward/punishment contingencies), we have likely changed the dynamics and difficulty of the task. Specifically, the crucial distinction for optimal performance changed from dissociating a 70/30 from a 30/70 cue, while in the 3-choice task, this required dissociating a 75/25 from a 50/50 option. We explore the effects of this change below.

In order to assess the impact of adding a neutral choice option on the reversal performance, we compared average behaviour of participants for 2-option version of the task (den Ouden et al. 2013, N = 204) and the current, 3-option, task. Supplemental *Figure S1A* displays average trial-by-trial choice probability for the mostly rewarded stimulus during the acquisition phase, which becomes the mostly punished stimulus during the reversal phase. For the 2-choice task, the ratio of reward/punishment for the Rewarded choice is 70:30 and in the current version it is 75:25. In both versions, participants learned to make the correct selection for the acquisition phase. However, reversal performance was much more rapid during the 3-choice task.

When fitting and comparing parameter estimates to both versions of the task for the winning Experience-Weighted Attraction (EWA) model (described in the main text), there was a striking difference in (inverse) learning rate parameter ϕ , which was much higher in the current 3-choice task. This meant that the effective learning rate was much lower, i.e. people

integrated information over a longer effective time window. In contrast, the winning experience weight parameter (ρ) and decision noise (β) estimates have very similar values (supplemental *Table S2*). This holds both when fitting the EWA model that was optimal in the 2-choice PRL task, but also when fitting the winning model for the 3-choice PRL task that included a forgetting factor (α_i).

Table S2. Median (25%-75% Range) parameter estimates for the 2- versus 3-choice PRL task. The key difference between the 2- and 3-option task is that the inverse learning rate parameter φ is much larger (i.e. slower learning) for the 3-option model, while other parameter values were relatively unchanged.

Model	φ	ρ	β
2 option – EWA	0.33 (0.10 – 0.62)	0.62 (0.28 – 0.88)	4.69 (2.62 – 7.35)
3 option – EWA	0.56 (0.25 – 0.71)	0.51 (0.21 – 0.69)	3.16 (2.46 – 4.53)
3 option – EWA+F	0.77 (0.29 – 0.87)	0.63 (0.27 – 0.83)	4.23 (3.11 – 7.88)

A- Reversal performance for 2 and 3 option task

B - Performance score landscape for simulated data as a function of inverse learning rate (φ) and experience accumulation rate (ρ)

Figure S1. A. Reversal performance for 2 and 3 option task. Trial-by-trial averaged probability of selecting the stimulus S_1 , which was mostly rewarded during the acquisition phase and punished during the reversal phase. For illustration, we used a sliding window with 5-trial width. Participants learned to make the correct selection for the acquisition phases in both task, but showed relatively rapid reversal during the 3-option task. The dashed lines indicate chance level choice for each task. Note that the 2-option task had a fixed feedback sequence while the 3-option version did not, resulting in smoother curves when averaging over participants. **B. Performance score landscape for simulated data as a function of inverse learning rate (φ) and experience accumulation rate (ρ).** The key observation is that the range of optimal φ is much wider for the 2-option relative to the 3-option model, where for the latter, performance steeply drops off as soon as φ decreases. Also, note also that ‘forgetting’ of the unchosen option helps performance in both task versions. Importantly, the pattern of performance score sensitivity as a function of φ is constant across the models (with and without forgetting).

Reduced optimal learning rate in 3-choice PRL task

In order to quantify the intuition that whether this change in learning rate was adaptive in the novel task, we computed the optimal learning rate for each task version, for both winning models (EWA vs. EWA with forgetting). In order to find the optimal values for ϕ and ρ we simulated performance score for the entire [0 1] range of these two parameters with step size = 0.05. For all other parameters we used the median value of the fitted parameters across participants (EWA: $\beta=4.5$ and EWA+F: $\beta=4.5$ and $\alpha_f=0.35$). We ran 100 simulations for each parameter set. We computed a (normalized) performance score based on the likelihood of receiving positive feedback for each of the stimulus options:

2-choice PRL task

$$Performance = \frac{(0.70 \times N_{Rewarded} + 0.30 \times N_{Punished}) - 0.30 \times N_{Trials}}{0.70 \times N_{Trials} - 0.30 \times N_{Trials}} \times 100 \quad (1)$$

3-choice PRL task

$$Performance = \frac{(0.75 \times N_{Rewarded} + 0.50 \times N_{Neutral} + 0.25 \times N_{Punished}) - 0.25 \times N_{Trials}}{0.75 \times N_{Trials} - 0.25 \times N_{Trials}} \times 100 \quad (2)$$

where $[N_{Rewarded} N_{Neutral} N_{Punished}]$ is the number of trials which each stimulus is selected and N_{Trials} is the total number of trials (80 for both tasks). The performance score normalized to a minimum of 0 when the punished stimulus was chosen on all trials, and a maximum of 100 when the rewarded stimulus was chosen on all trials.

In line with the observed participant behaviour across the two tasks, subjects show a lower effective learning rate (high ϕ) for the 3-option than the 2-option task. Moreover a higher learning rate (low ϕ) was associated with lower performance scores (*Figure S1B*). In contrast, for the 2-choice model the range of learning rates that result in optimal performance is much wider. This optimal lower learning rate in the 3-option task can be understood when realising that optimal performance on the 3-choice tasks requires participants to dissociate between a 50/50 and a 75/25 reward/punishment cue. In contrast, in the 2-choice task the key dissociation was between a 70/30 and 30/70 cue. For the latter, integration over fewer choice-outcome observations, i.e. a narrower window to the past, so a higher learning rate, is required to distinguish the optimal action. Of note, this reduction in learning rate is also reflected in the raw behavioural scores, with a much lower tendency to shift following a loss. Indeed, lose-shift behaviour is below chance level, meaning that even after a loss, people are more likely than chance to repeat their previous choice (cf. *Figure 1*, main text), compared to above-chance lose-shift rates in the 2-option task (c.f. *Figure 2B*; den Ouden et al. 2013).