Assessing the influence of dopamine and mindfulness on routines in visual search

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Abstract

Given experience in cluttered but stable visual environments, our eye-movements adapt to form stereotyped routines that frequent the locations most likely to offer task-relevant information, while not confusing routines between similar task-settings. Theoretical insights suggest that dopamine function and mindfulness may be important modulators of the formation and deployment of such routines, yet quantification of their impact remains to be tested in healthy humans. Over two sessions, participants observed a gaze contingent display comprised of a 4 x 4 grid of doors, and were instructed to use their eyes to open doors in order to find hidden targets. Within each session, doors appeared in either one of two colours, with colour signalling differing likely target locations (task-settings). We derived measures for how well participants learned the target locations (accuracy), how routine was their deployment of eye-movements (stereotypy), and how much participants confused settings (setting accuracy). Participants received either Maladopar (dopamine precursor) or placebo (vitamin C) across the 2 sessions, administered under double-blind conditions. Dopamine and trait mindfulness (assessed by questionnaire) interacted to influence both accuracy and stereotypy. Increasing dopamine improved accuracy and reduced stereotypy for individuals scoring high for mindfulness, and induced the opposite pattern for low mindfulness scorers. Dopamine also disrupted setting accuracy invariant to mindfulness. The data suggest that mindfulness modulates the impact of dopamine on the formation of stereotyped eye-movement routines; low mindfulness may cause settling on suboptimal routines at the expense of learning. Increasing dopamine promotes confusion between task-settings, regardless of mindfulness. These findings provide a link between non-human and human models regarding the influence of dopamine on the formation of task-relevant eye-movement routines, and provide novel

insights into behaviour-trait factors that modulate the use of experience when building adaptive repertoires.

***K*eywords** habit · sequence · dopamine · mindfulness · eye-movements

1 Introduction

Given stable environmental contingencies, it is adaptive for an organism to develop routine ways of performing tasks requiring multiple responses. Dopamine is assumed to play a key role in the neural computations that underlie the formation of task routines. A large body of evidence shows that dopaminergic midbrain neurons encode reward prediction errors (e.g. Schultz, Apicella, and Ljungberg 1993; Hollerman and Schultz 1998; Waelti, Dickinson, and Schultz 2001), a teaching signal assumed to compute the value of actions (Sutton and Barto 2018). A comparable signal in striatum marks the difference between expected and actual saccadic sequence lengths used by macaques to attain reward during visual search (Desrochers et al. 2010; Desrochers, Amemori, and Graybiel 2015). This signal is assumed to reflect a cost-benefit signal that computes the value of saccadic routines. There also exists a large body of evidence from rodent and macaque models suggesting that increased striatal dopamine availability speeds the transition from goal-directed to habitual control of behaviour (Harmer and Phillips 1998; Nelson and Killcross 2006; Nadel et al. 2021, 2021), the latter of which is assumed to govern performance of routines (Dezfouli and Balleine 2012; Dezfouli, Lingawi, and Balleine 2014; Desrochers, Amemori, and Graybiel 2015; Graybiel and Grafton 2015; Smith and Graybiel 2016). Although this evidence implicates dopamine in the formation of task-relevant routines, whether dopamine availability modulates the formation of saccadic routines in healthy humans remains an open question.

One way to address this question is to increase dopamine availability via administration of L-Dopa, a precursor to dopamine. L-Dopa administration in humans has been associated with elevated positive prediction errors in striatal blood-oxygenation-level-dependent BOLD responses (Pessiglione et al. 2006) and with reduction of explorative choices during instrumental learning (Shohamy et al. 2006; Chakroun et al. 2020). This suggests that L-Dopa may increase the perceived value of performed actions by inducing optimistic evaluations of outcomes (FitzGerald, Dolan, and Friston 2015), possibly by disrupting feedback processing (Shohamy et al. 2006). Elevating dopamine availability via L-Dopa may therefore have a comparable impact on the cost-benefit computations driving the formation of saccadic routines during visual search. Specifically, L-Dopa may promote an optimistic evaluation of the performed sequence, increasing the probability that it is adopted as a routine.

For task-oriented routines to be adaptive, it is also required that they are not confused between tasks, despite overlap in the situational cues that mark task environments. Dopamine is assumed to play a modulatory role in the activation of task-relevant behaviours in response to relevant situational cues (Budzillo et al. 2017), as well as promoting the formation of routines. Patients with Parkinson's Disease consistently show deficits switching between simple sensorimotor tasks (Cools et al. 2001; Wiecki and Frank 2010), as do healthy participants who have been administered D2 antagonists (Mehta et al. 2004). Such findings have been accounted for by assuming that decreased dopamine causes increased uncertainty about the probability of being in a specific task-state (Friston et al. 2012). These assumptions are based on evidence from constrained tasks - i.e. when single correct responses are required for given stimuli. In contrast, saccadic routines are often formed from a self-selected set of many possible eye-movements, and it is unclear whether dopamine modulates confusion between routines. If an impact is observed, it is unclear whether the effect is opposite to that of depleted dopamine, i.e. does increasing dopamine availability promote segregation of task routines? Or, does increasing dopamine availability make it more difficult to switch between routines, thereby creating confusion between them?

A further but less frequently discussed component of the processes underlying task routine learning and deployment, is the brain's representation of task-relevant cues and actions, presumably encoded by cortex and relayed to striatum for reinforcement (Wickens et al. 2007; Ashby, Turner, and Horvitz 2010; Bar-Gad et al. 2000; Kirk et al. 2014, 2019). Presumably, the organism that encodes an accurate representation of cues, actions and outcomes is at an adaptive advantage when forming and deploying task-relevant routines. A growing body of empirical evidence suggests that mindfulness may modulate fidelity of such representations. Theoretically, mindfulness has been defined as a mental state that emphasises current sensory and internal inputs (Davids 1900; Shapiro et al. 2006), and as such is well-placed to promote accurate task-representations. In support of this notion, mindfulness practice has been associated with increased error monitoring during cognitively challenging tasks (Andreu et al. 2017), and with greater sensitivity to dynamics in operant reinforcement contingencies (Chen and Reed 2023; Reed 2023). This suggests that increased mindfulness

corresponds to a more precise representation of the stimulus and response elements that make up the task-state.

What could be the modulatory influence of mindfulness on the formation and deployment of task-relevant routines? Mindfulness appears to have opposing influences to dopamine on routine learning and task-switching: individuals low in trait mindfulness are faster to exploit sequential regularities in stimulus-response tasks (Stillman et al. 2014), and exploitation of such regularities are assumed to support habitual responses (Dezfouli and Balleine 2012; Dezfouli, Lingawi, and Balleine 2014). Mindfulness may also promote task-switching; higher levels of trait mindfulness has been associated with decreased reliance on past behaviours when stimuli are conserved across tasks that carry different cognitive demands (Greenberg, Reiner, and Meiran 2012; Kuo and Yeh 2015). Indeed both reinforcement learning (RL) and active inference frameworks have been used to posit common but opposing mechanistic actions for both mindfulness and dopamine. In the case of RL, mindfulness is assumed to attenuate striatal reward prediction errors (Kirk and Montague 2015; Kirk et al. 2019), possibly via greater regulation from stronger cortical representations of subjective values and internal states (Kirk et al. 2014). In the case of active inference, both dopamine (Friston et al. 2012; FitzGerald, Dolan, and Friston 2015) and mindfulness (Laukkonen and Slagter 2021; Giommi et al. 2023) are assumed to modulate the estimate of uncertainty that is used to weight task-relevant prediction errors. These lines of evidence suggest that high trait mindfulness may negate the impact of elevated dopamine on task-relevant routines, yet it remains to be ascertained whether these assumed links are borne out in a quantitative test.

Thus, using a novel task designed to test the formation and deployment of task-relevant saccadic routines in humans, we sought to test whether administration of L-Dopa increased suboptimal routine formation, and whether increased dopamine positively or negatively modulated switching between routines. Last we sought to test whether higher levels of trait mindfulness offered a buffer against the impacts of increased dopamine availability. To preview the results, L-Dopa decreased accuracy and promoted routine formation in individuals with low trait-mindfulness, whereas high trait-mindfulness was associated with the opposite pattern. Regardless of mindfulness, dopamine hampered switching between routines by increasing routine confusion.

2 Methods

2.1 Participants

A total of 40 participants (mean age: 24.5, sd: 5, 30 female, 10 male) were recruited using the undergraduate and paid SONA pools administered by the University of Queensland. All procedures were cleared by the University of Queensland Human Research ethics committee [2017/HE000847], and were conducted in accordance with the National Statement on Ethical Conduct in Human Research. Participants were over 18 years old, had no known neurological and psychiatric conditions (assessed by self report), and no contraindications to Levodopa, as assessed by the Levodopa safety screening questionnaire. Informed consent was obtained at the start of the first session.

2.2 Procedure

Participants attended two sessions, spaced approximately 1 week apart. After initial blood pressure (BP) and mood assessments (Bond and Lader 1974), participants received either placebo (vitamin C) or Levodopa (Madopar 125: 100 mg Levodopa and 25 mg Benserazide Hydrochloride), crushed and dispersed in orange juice, now referred to as the 'placebo' and 'DA' sessions respectively. The solution was prepared by an experimenter who did not administer the remaining experimental procedures. This protocol was sufficient to achieve double blinding in previous work (Chowdhury et al. 2012, 2013). Participants then completed the Five Facet Mindfulness Questionnaire (Baer et al. 2006) and the Barratt Impulsivity Scale [BIS; Patton, Stanford, and Barratt (1995)], as trait impulsivity scores are associated with midbrain dopamine D2/D3 receptor availability (Buckholtz et al. 2010). Around 30 minutes after drug administration, participants completed a second BP and mood rating assessment. Participants then completed the practice stage of the task, so that the experimental stage began approximately 40 minutes after drug ingestion, within the window of peak plasma availability [Li-Ann, do you have a ref?]. At the end of the session, participants completed the final BP and mood rating assessment and were asked whether they thought they had been given the active or placebo drug.

2.3 Apparatus

The experimental task was run with custom code[1], written using Matlab 2012b (32 bit) and Psychtoolbox v3.0.14, on a Windows 7 (64-bit) on a Dell Precision T1700 desktop computer, displayed using a ASUS VG248 monitor. Gaze coordinates (x, y) were sampled at 120 Hz using a monitor-mounted iView Red-m infrared eye tracker (SensoMotoric Instruments GmbH, Teltow, Germany). Participants were seated from the monitor at an approximate viewing distance of 57 cm, and positioned on a chin-rest for the duration of the task.

2.4 Experimental Task

Each trial began with a fixation dot presented centrally on a grey screen [RGB: 200 200 200]. Participants were instructed to fixate on the dot to begin a trial. After 1000 ms of continuous correct fixation samples (within 100 pixels of fixation), a square was presented that comprised 18° of degree visual angle along each length. The square could be one of four possible colours [RGBs: 87, 208, 169; 267, 145, 52; 167, 162, 229; 239, 91, 158]. After 1000 ms, a 4 x 4 grid of smaller squares appeared within the larger square, in a darker version of the background colour ([RGB]-50). Each square comprised 2.6° of visual angle. Participants were instructed that the 4 x 4 grid represented doors, and that they were to use their eyes to open the doors to find where the target was hiding. Participants were also instructed that they were to fixate on a single door to open it. When participants had fixated on a door for over 300 ms, the door either turned black [RGB: 50, 50, 50], to denote the absence of a target, or the target was displayed and the trial was terminated. If the door had turned black, it returned to its previous colour as soon as it was detected that the participant had moved their eyes from the door. Targets were animal images drawn randomly on each trial from a pool of 100 images taken from the internet. The time at which the target was available to be found varied from trial to trial, with the onset being drawn from a uniform distribution between 500-2000 ms. Once the target was available and the correct door selected, the target was displayed for 750 ms. Upon termination of the trial, the grey screen and white fixation cross were presented (see Fig **??**A).

In each session, participants saw the display in two possible colours. Participants were instructed that each colour represented a world, and that the animals had different places they preferred to hide, depending on the world they were in. There were four possible target locations within each world, or from here on, each setting. For each setting, 1 door from each quadrant was selected as one of the 4 possible target locations (see Fig **??**B), with the constraint that target locations could not overlap between settings. Thus each colour reflected a setting in which participants could establish a set of task-relevant eye-movements, i.e. towards the 4 possible target locations. Note that within each setting, the target was equally likely to appear behind any one of the 4 target doors (p=.25) and would never appear behind the remaining doors (p=0). Colour-target location mappings were counterbalanced across participants, as was the assignment of colours to sessions. Participants completed 80 trials in each setting. Eye-movement calibration and validation was performed every 20 trials. Participants were also shown the standard QWERTY keyboard and were instructed that they could press 'x' at any time to perform a new calibration and validation if they felt that their eye-movements were no longer being registered accurately.

2.5 Statistical Approach

The analysis was designed to assess how well participants learned the target locations, the extent to which participants formed a routine for door selections - i.e. how stereotypical they became in their order of door-selections, and how well they disambiguated between settings. We modelled how these elements of performance were modulated by the dopamine and mindfulness factors. All custom analysis code is available online[2]. The analysis was performed using R and RStudio v2022.07.2 (RStudio Team 2020), and can be reproduced in the Neurodesk container environment (Renton et al. 2022).

2.5.1 Data cleaning

Doors were marked as selected if participants gazed at them for a duration of at least 300 ms. We assumed that a door could not be selected twice consecutively, and collapsed any consecutive selections into a single door selection. Last, as the final door selection of every trial was fixed (i.e. finding the target location ends the trial), we removed the final selection from each trial for the stereotypy (routine) analysis defined below. We excluded data from one participant whose total number of door selections was greater than 3 standard

[1] `https://github.com/kel-github/variability-decision-making`
[2] `https://github.com/kel-github/DA_VisRoutes`

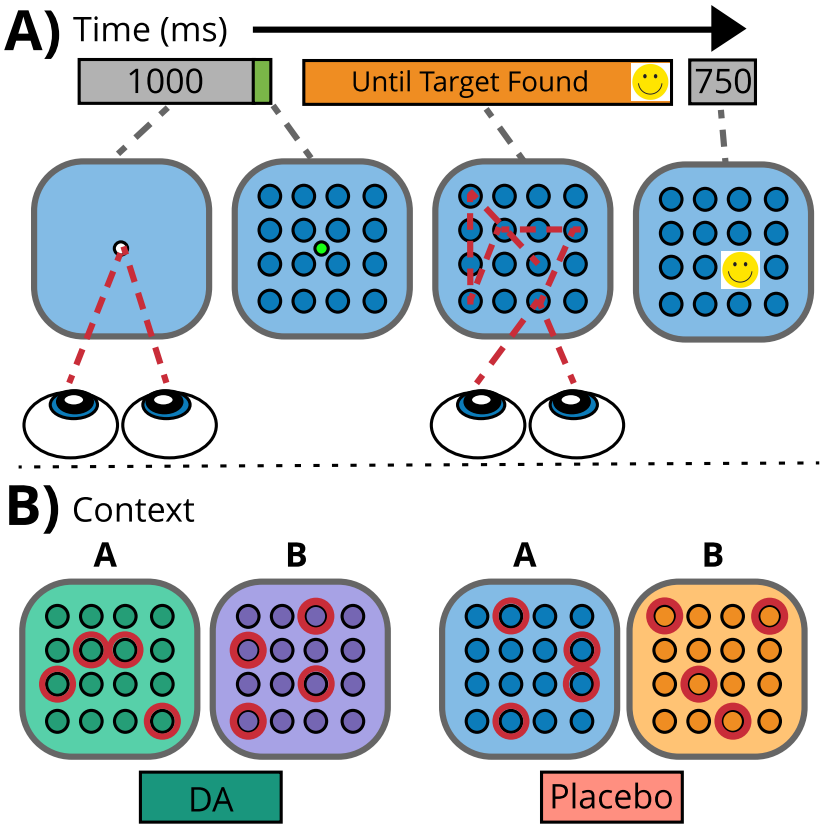

Figure 1: Experimental Task. A) A single trial where participants use their eyes to open doors to locate a target. B) Contexts and sessions: in each session, participants are exposed to two colour contexts each with 4 unique and equiprobable target locations. Colours and target locations were counterbalanced across participants and sessions. In each session, Levodopa (DA) or placebo is administered under double blind conditions.

deviations from the mean across both sessions. The remaining 39 datasets were retained for all of the analyses. Note that this is more inclusive than our pre-registered plan for data exclusions[3]. Based on pilot data, we had planned to exclude participants who scored $< 65\%$ accuracy over the course of a session. Analysis of the final sample suggested that this was too stringent, as this resulted in the exclusion of 14 of 40 participants.

2.6 Accuracy

We first sought to determine the extent to which L-Dopa and mindfulness influenced the learning of target locations across settings (accuracy). To compute a measure of accuracy, door selections were classified as target relevant (TR) for the current setting (i.e. the setting presented on trial_{t}, cs), the other setting from that session, not presented on trial_{t} (os), or neither (n). Note that early in task learning, an 'os' response is a reasonable guess and should not be classified as incorrect (i.e. n). The group level mean probabilities of cs, os and n responses are presented in supplementary Figure X. Data was grouped into blocks of 10 trials per setting, and grouped across settings, resulting in 8 blocks of 20 trials. We defined accuracy (acc) as the number of times participants selected a target door from either setting, relative to all door selections:

$$acc = \frac{\sum(TR_{cs}, TR_{os})}{\sum(TR_{cs}, TR_{os}, n)}$$

[3] `https://osf.io/2y6pk`

We assessed the influence of block, drug and mindfulness on accuracy using a Bayesian mixed model approach. Accuracy was assumed to be drawn from a binomial distribution (1=target door, 0 = non-target door). We then model the logit function of the probability of drawing a target-door from the total number of door selections. Note that resulting regression parameter values reflect changes to the log-odds of target door selections.

For this and following analyses, we identified the model that best fit the data, and made inference over the resulting parameters. We report the 95% confidence intervals (CIs) of the parameter posteriors, and assume a reliable effect when the 95% CIs of the posterior do not include zero. Models were fit using the BRMS (Bürkner 2017) interface for Stan (Team, n.d.) and RStan (Stan Development Team 2023). We used the default weakly informative priors as specified in (Bürkner 2017). Specifically, fixed and random effect β coefficients were given a flat prior, intercept and standard deviations were assumed to be drawn from a student's t distribution (df=1, location=0, scale=2.5), and the LKJ-correlation prior with parameter $\zeta > 0$ was used for the parameter covariance matrix. For each model, we checked for parameter recovery using simulated data. Once fitted, we checked that the residuals showed no signs of systematic error, that the chains had converged, and that $\hat{R}$ values were less than 1.01.

To eschew an overly large model space, and in line with our pre-registration, we first fit models that contained each possible combination of the block and drug regressors (and associated random effects), and found the best model using leave-one-out (LOO) cross validation (as implemented in Vehtari, Gelman, and Gabry 2017). (Note that in the pre-registration document we had proposed to compare models using the deviance information criterion (DIC). As LOO is more robust than DIC to influential observations, and is readily implemented for use with BRMS model objects, we opted to use LOO instead of DIC). Upon identifying the best model, we then added the mindfulness regressor using all possible combinations, and once again selected the best model (as evidenced by LOO). Last we controlled for trait impulsivity by adding BIS scores as a main effect to the winning model. Note that in no cases did adding BIS scores improve the model. We report the difference in the expected log posterior density (ELPD) between the next best models and the winning model, and the ratio of the ELPD difference to the standard error (SE) of the difference (ELPD:SE), thus a negative ELPD difference reflects preference for the winning model. The full set of model comparisons are presented in the supplementary materials.

2.7 Setting Accuracy

We next sought to model the impact of L-Dopa and mindfulness on task confusion. To measure the extent of task confusion, we computed a measure of setting accuracy (s-acc). This measure indexes how often participants selected a door that was relevant for the colour setting displayed on trial t (current setting, cs), relative to how often they selected a door that was relevant for the setting not displayed on trial t (i.e. the other setting from that session, os):

$$s{-}acc = \frac{\sum TR_{cs}}{\sum (TR_{cs}, TR_{os})}$$

We modelled the influence of L-Dopa and mindfulness on s-acc using the Bayesian mixed effects approach described above (Note that in the pre-registration document we had suggested to include a regressor for context. Visual inspection of the data showed that s-acc was highly comparable across contexts [see supplemental figures]. We therefore opted to simplify the model space and collapse over this factor).

2.8 Stereotypical door selections

Next, we determined the extent to which door-selections became routine over the course of the task - specifically, how much the order of door selections increased in stereotypy, and whether dopamine and mindfulness modulates the extent of stereotypy. Here we use stereotypy as a proxy for routine formation, and we define stereotypy as the tendency to choose doors in the same order, over trials (e.g. Desrochers, Amemori, and Graybiel 2015).

In order to index stereotypy, we reasoned that stereotypy should result in an increase in the probability of a subset of door transitions. This stands in contrast to when making door selections in an entirely exploratory, or non-stereotyped way, where there should be an even representation of door transition probabilities. Therefore, the transition probability matrices of individuals engaged in more stereotypical door selections should show higher variance than those who are not engaging in stereotypical door selections. We therefore computed

trial level transition probability matrices, and computed the variance of each matrix. Variances were then collapsed across settings and trials to form a stereotypy score for each participant, session and block.

The resulting stereotypy scores were subject to a comparable Bayesian mixture modelling approach as described above with a few key differences; the stereotypy scores were assumed to be drawn from a skewed normal distribution $\mathcal{N}(\mu, \sigma, \alpha)$ whose mean (μ) was defined by the regression parameters (the distribution of variance scores can be found in the supplemental materials). σ was assumed to be drawn from a Student's t distribution (df=3, location=0, scale=2.5), the skew parameter (α) was assumed to be drawn from a normal distribution $\mathcal{N}(0, 4)$. The remaining priors for the intercept, beta-coefficients and parameter covariance matrix were defined in the same manner as for the accuracy data models. As the log-log plot of variances vs block suggested a power function, analysis was performed on the logged data. This ensured that the relationship between block and variance values was best described by a straight line. Identification of the winning model proceeded as described for the accuracy data above.

2.9 Blinding analyses

To determine whether awareness of the dopamine intervention could have contributed to the findings, the probability of participant ratings were compared to the expected values assuming chance guessing, using a Chi Square test. BP and mood ratings were each subject to a session (DA vs placebo) x timepoint (pre-drug, pre-experiment, post-experiment) Bayesian repeated measures ANOVA, implemented using the BayesFactor package for R (Morey, Rouder, and Jamil 2015) using the default priors (Rouder et al. 2012).

3 Results

Overall, mindfulness and DA interacted to show opposing effects on accuracy and stereotypy, whereas only DA modulated setting accuracy.

3.1 Accuracy

3.1.1 Model Selection

First we sought the best model in order to make subsequent inference over the parameters. The model that best accounted for the experimental factors contained main fixed effects of block and drug, and random effects for block x drug. Although this model was only closely preferred to the next most complex model that contained a block x drug interaction (ELPD diff = -0.17, ELPD:SE = -0.32), it was strongly preferred to all other models (min ELPD diff = -674.10, ELPD:SE = -8.35). Adding mindfulness scores improved the predictive accuracy of the model; the winning model contained a 3-way block x drug x mindfulness interaction (and associated two-way interactions and main effect of mindfulness; ELPD diff = -12.02, ELPD:SE = -1.88). Adding BIS scores did not improve the predictive value of the model (ELPD diff = -0.16, ELPD:SE = -0.34). Note that although we draw inferences over parameters from the winning model, our inferences are the same as if we had used the more complex model that includes the BIS scores.

3.1.2 The effect of DA and mindfulness on accuracy

Having established the best model to account for the data, we next determine the influence of DA and mindfulness on accuracy by making inference over the resulting parameters. Accuracy data plotted by block x drug session (DA va placebo) are shown in Fig 2A. Critically, the influence of drug on accuracy was impacted by mindfulness scores. The drug x mindfulness parameter differed reliably from zero (mean log odds = -0.11, 95% CI[-0.16, -0.06], see Fig 2E). To better understand this interaction, we computed a score for each participant that reflected the mean accuracy change due to the drug session (μ acc[DA - P]). Note that a positive score indicates that performance was better in the DA session relative to placebo. Next we examined the relationship between DA-induced accuracy changes and mindfulness scores. As can be seen in Fig 2B, there was a positive relationship between DA-induced accuracy changes and mindfulness; participants scoring higher for mindfulness showed higher accuracy in the DA relative to the placebo session, for example, those scoring in the highest quartile showed mean accuracy scores of 0.67 (95%CI[0.65, 0.70]) during the DA session, relative to mean accuracy scores of 0.62 (95% CI[0.60, 0.63]) during the placebo session. Individuals scoring low on mindfulness showed the opposite pattern (DA mean accuracy = 0.61, 95% CI[0.60, 0.63], placebo mean accuracy = 0.68, 95%CI[0.66, 0.69]), note that Fig 2B shows the difference between these accuracy scores). Thus the impact of DA on the establishment of task-relevant eye-movements is dependent on the mindfulness state of the individual.

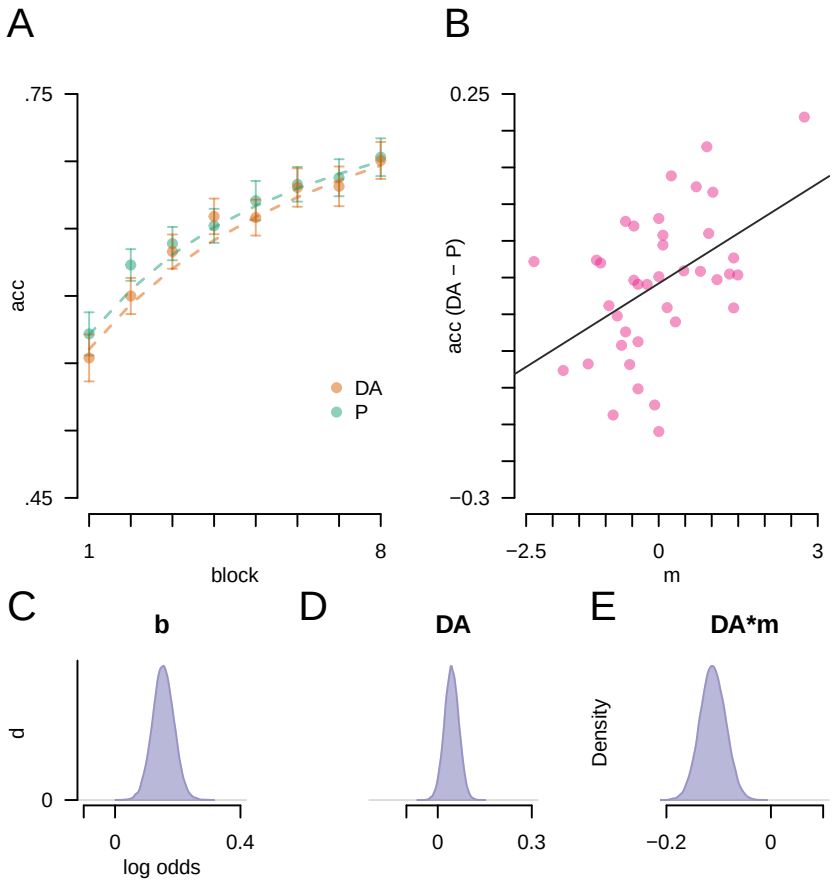

Figure 2: The influence of dopamine and mindfulness on accuracy. A) Accuracy (acc) data by block and drug. Circles reflect observed average accuracy, dotted lines reflect the fit of the winning model. B) The association between trait mindfulness (x-axis) and the impact of drug on accuracy [DA-P]. The bottom row shows posterior densities (in log odds) estimated for C) the main effect of block (b), D) the main effect of DA, and E) the drug x mindfulness (m) interaction. DA = dopamine, P = placebo, d = density. Error bars reflect within-subject standard error of the mean [SE].

Participants learned the target door locations over the course of the sessions, accuracy reliably increased over blocks. Mean accuracy in block 1 was 0.57 (95% CI[0.55, 0.59]), relative to a block 8 mean of 0.70 (95% CI[0.68, 0.72]). The model showed that accuracy increased by block with an average log odds of = 0.15, (95% CI[0.09, 0.22, Fig 2C). There was also the suggestion of a main effect of DA (mean log odds = 0.04, 95% CI[-0.001, 0.09, Fig 2D), however, the impact of DA accuracy is presumably better explained by the drug x mindfulness interaction.

3.2 Setting accuracy (s-acc)

3.2.1 Model Selection

The best model contained main fixed effects of block and drug, and random effects for block x drug. Although this model was only closely preferred to the next most complex model that contained a block x drug interaction (ELPD diff = -0.66, ELPD:SE = -1.67), it was strongly preferred to all other models (min ELPD diff = -553.79, ELPD:SE = -8.35). Adding mindfulness scores improved the predictive accuracy of the model; the winning model contained an additional main effect of mindfulness (ELPD diff = -0.13, ELPD:SE = -0.12). Adding BIS scores did not improve the predictive value of the model (ELPD diff = -0.02, ELPD:SE = -0.03). Note that although we draw inferences over parameters from the winning model, our inferences are the same as if we had used the more complex model that includes the BIS scores.

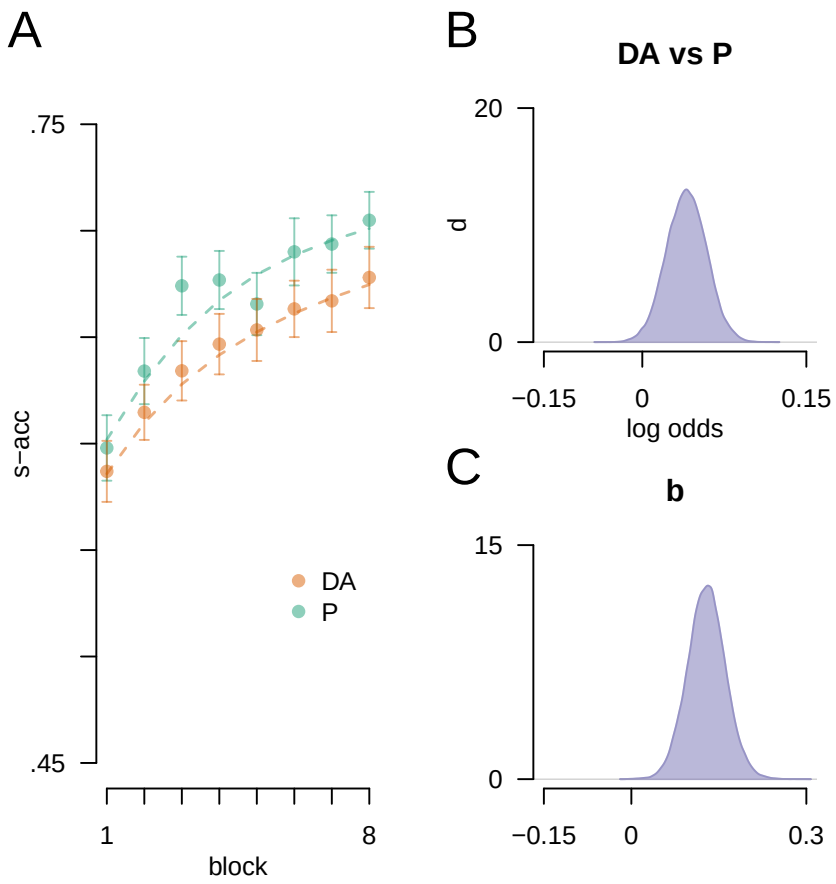

Figure 3: The influence of dopamine and mindfulness on setting accuracy. A) Accuracy (acc) data by block and drug. Circles reflect observed average accuracy, dotted lines show the fit of the winning model. B) Estimated posterior density (in log odds) for the main effect of drug (DA vs P), D) same as in B, but for the main effect of block. DA = dopamine, P = placebo, b = block, d = density. Error bars reflect within-subject standard error of the mean [SE].

3.2.2 Drug, and not mindfulness, impacts setting accuracy

We next determined the influence of DA and mindfulness on setting accuracy by making inference over the resulting model parameters (see Fig 3. DA reduced setting accuracy; accuracy was on average 0.64 (95% CI [0.63, 0.65]) for the DA session, and 0.66 (95% CI [0.65, 0.68]) for the placebo session. The log-odds of selecting a target door that was specific to the current context increased by a mean log odds of 0.07 (95% CI[0.01, 0.13, Fig 3A&B) for the placebo session, relative to the DA session. This suggests that DA causes confusion between settings.

Setting accuracy improved over the course of each session; mean accuracy in block 1 was 0.59 (95% CI[0.58, 0.61]), relative to block 8 (mean: 0.69, 95% CI[0.67, 0.71]). The model showed that setting accuracy increased by a mean log odds of 0.13 (95% CI[0.07, 0.19) over each block (Fig 3C). In contrast to the overall accuracy data, mindfulness did show a reliable impact on setting accuracy (mean log odds = 0.04, 95% CI[-0.04, 0.15]).

Setting Accuracy Control Analysis DA influences contextual accuracy, which indexes the likelihood of cs door selections, over os door selections. As we exclude door selections for locations that are never target relevant (n) from the computation of setting accuracy, it is important to verify that setting accuracy scores do indeed reflect confusion between settings (cc + oc), rather than a general task learning deficit. To address this in an exploratory analysis, we reasoned that if setting accuracy scores reflected a general deficit, then 'error' door selections (i.e. non-cs selections) should be drawn randomly from the remaining doors (os = 4 & n = 8). Therefore, when considering only os and n door selections, a general deficit interpretation suggests that os doors should be selected from this total set (oc + n) with $p = .\overline{333}$, i.e. at chance. If setting accuracy

scores do tap setting confusion, then os doors should be selected at a level that is higher than chance. To test this, we computed for each participant the probability of os selections, given the set of os and n (p_{os}), and performed a one-sided t-test, against a null value of $p = .333$. (Note that we opted to use an NHST approach as we had a point null hypothesis). The p_{os} data was unlikely under the null hypothesis (mean = 0.37, 95% CI[0.35, 0.39], $t(38) = 3.62$, $p = 0.0004$. Therefore, we reject the hypothesis that the DA induced drop in setting accuracy reflects a general learning deficit.

3.3 Stereotypy of door selections (routine)

3.3.1 Model Selection

The model that best accounted for the stereotypy data contained main fixed effects of block and drug, and random effects for block x drug. Although this model was only closely preferred to the next most complex model that contained a block x drug interaction (ELPD diff = -0.26, ELPD:SE = -1.29), it was strongly preferred to all other models (min ELPD diff = -130.14, ELPD:SE = -7.71). Adding mindfulness scores improved the predictive accuracy of the model; the winning model contained an additional main effect of mindfulness and a drug x mindfulness interaction (ELPD diff = -3.15, ELPD:SE = -0.92). Adding BIS scores did not improve the predictive accuracy of the model (ELPD diff = -0.54, ELPD:SE = -1.41). Note that although we draw inferences over parameters from the winning model, our inferences are the same as if we had used the more complex model that includes the BIS scores.

3.3.2 The impact of drug and mindfulness on stereotypy

Mindfulness and dopamine interacted to impact stereotypy; we observed a reliable drug x mindfulness interaction (mean $\beta = 0.11$, 95% CI[0.02, 0.21, Fig 4). Mindfulness scores modulated the stereotypy difference between the DA and placebo sessions; for example, those scoring in the highest quartile showed mean log variance scores of -8.74 (95%CI[-8.80, -8.68]) during the DA session, relative to mean log variance scores of -8.68 (95% CI[-8.74, -8.62]) during the placebo session. Individuals scoring low on mindfulness (lowest quartile) showed the opposite pattern (DA mean accuracy = -8.69, 95% CI[-8.75, -8.63], placebo mean accuracy = -8.72, 95%CI[-8.78, -8.66]). To visualise this interaction, we computed a mean variance change score between drug sessions for each participant (μ stereotypy[DA - P]). Note that a positive score indicates that performance was more stereotyped in the DA session relative to placebo. As can be seen in Fig 4B, there was a negative relationship between drug-induced stereotypy changes and mindfulness. Thus the impact of DA on the formation of eye-movement routines is dependent on the mindfulness state of the individual.

Participants developed routines over the course of the experiment, as evidenced by a reliable increase in stereotypy over blocks (mean increase per block: $\beta = 0.32$, 95% CI[0.20, 0.43, Fig 4C). In line with the interaction of drug x mindfulness reported above, the main effect of mindfulness suggested a negative relationship with stereotypy (mindfulness mean β = -0.15, 95% CI[-0.26, -0.05, Fig 4D). Overall, higher mindfulness scores predicted less stereotypy in door-selection patterns relative to low mindfulness scores.

On the relationship between accuracy and stereotypy Accuracy and stereotypy showed opposing relationships with mindfulness and DA - higher mindfulness scores were associated with a beneficial influence of DA on accuracy, and lower levels of stereotypy, relative to placebo, whereas individuals scoring low on mindfulness showed a deleterious influence of DA on accuracy, coupled with increased stereotypy, relative to placebo. As accuracy and stereotypy are possibly, but not necessarily related, we next sought to ensure that the observed influences of DA and mindfulness on stereotypy was not being driven by accuracy, in an exploratory analyses. First we reasoned that such a pattern of results could be observed if the measures of accuracy and stereotypy reflected a direct trade off; i.e. as accuracy goes up, stereotypy goes down. A correlation analysis ruled out this possibility. We computed mean accuracy and stereotypy scores for each participant, collapsing across all experimental factors, and found that accuracy and stereotypy were positively related ($r(37) = 0.72$, $p = 2.45\text{e-}07$). Next, to rule out the contribution of accuracy to the stereotypy results, we added mean accuracy, computed for each block and drug condition, as a regressor to the winning model. Adding accuracy as a regressor both clearly improved the predictive accuracy of the model (ELPD diff = -110.26, ELPD:SE = -6.12), and served to increase certainty in the interactive influence of mindfulness x drug on stereotypy. Specifically, the estimated influence of the interaction increased from $\beta = 0.11$ to $\beta = 0.22$ (95% CI[0.14, 0.29]). Note that the pattern of remaining results were also consistent between the two models. Therefore, the data support the notion that mindfulness and DA interact to differently influence accuracy and stereotypy when participants perform task-relevant saccadic routines.

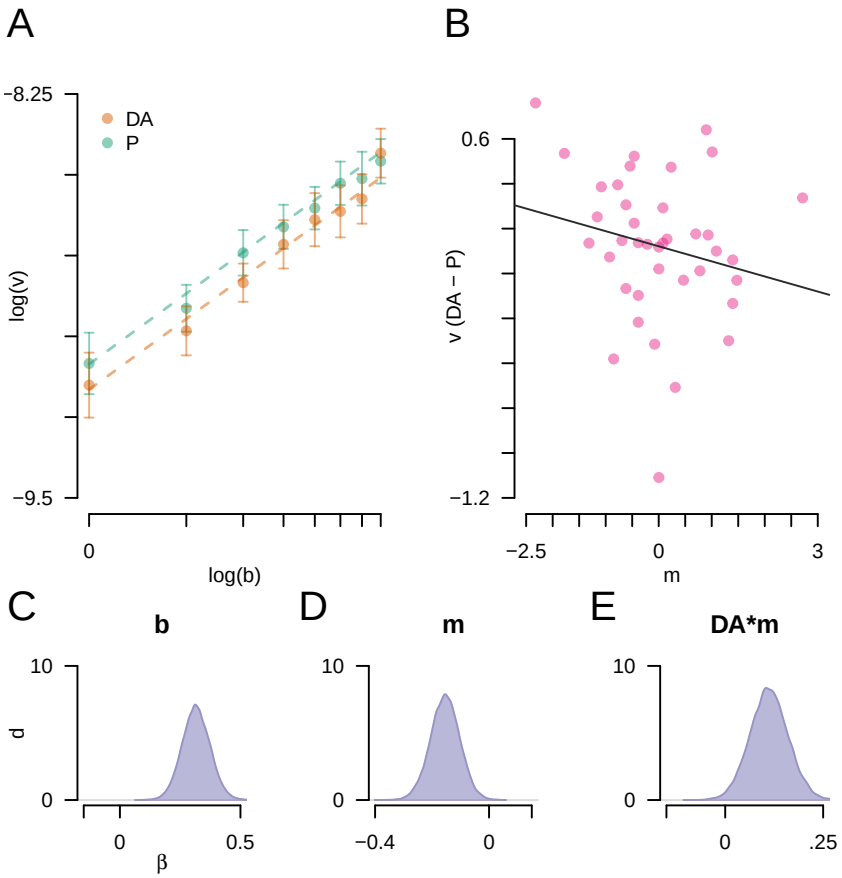

Figure 4: The influence of dopamine and mindfulness on door selection stereotypy. A) Accuracy (acc) data by block and drug. Circles reflect observed average variance (of the transition matrices), dotted lines show the fit of the winning model. B) The association between trait mindfulness (x-axis) and the impact of drug on variance [DA-P]. The bottom row shows posterior densities (in log odds) estimated for C) the main effect of block (b), D) the main effect of DA, and E) the drug x mindfulness (m) interaction. DA = dopamine, P = placebo, d = density. Error bars reflect within-subject standard error of the mean [SE].

3.4 Blinding check

Next we checked if participants knew whether they had received Levodopa or placebo across the two sessions. Participants were asked to report at the end of each session whether they thought they had received Levodopa or placebo. Participant responses were coded as either correct for both sessions (cc: observed N = 7), correct for one session and incorrect for the other (ci: N = 11), or incorrect for both sessions (ii: N = 8). The probability of the observed guesses was not statistically unlikely given the null distribution of chance performance (the null hypothesis specified p= .25, .5, .25 for cc, ci, ii respectively, $\chi^2(2, 26) = 0.69$, p =0.71). Note that we were unable to include all the participants in this analysis owing to missing data. Specifically, due to a miscommunication in the research team, the blinding check questions contained 'Don't know' as a possible response, for which we are unable to generate a null hypothesis. We therefore only include participants who made a guess using the Levodopa and placebo options across both sessions.

3.5 Mood and Blood Pressure

We also sought to determine whether DA influenced physiological factors such as mood and BP. For mood, the winning model contained a main effect of time-point and no other fixed effects. This model was preferred relative to next best model, which contained an additional main effect of drug (BF = 3.76, ±2.14%) and was substantially preferred over the null random intercept model (BF = 514549 ±1.23%).

Mean blood pressure was computed using the formula: Mean BVP = diastolic blood pressure (DBP) + 1/3 [systolic blood pressure (SBP) – DBP]. For mean BVP, the winning model contained main effects of both time-point and drug. This model was barely preferred to the next best model which contained a time-point x drug interaction (BF = 1.7 ±5.69%), but was strongly preferred to the random intercept model (BF = 5011975 ±3.76%). Overall, mean BVP was lower in the Levodopa session (mean = 2.181.511261, 95% CI[80.3, 82.8]), relative to placebo (mean = 84.5, 95% CI[83.5, 2.185.504042]).

4 Discussion

We investigated the impact of L-Dopa administration and trait mindfulness on the learning of task-relevant behaviour sets, and on the routine nature of their deployment. Participants opened doors to search for targets in a gaze-contingent display. The colour of the display signalled likely target locations, making some locations relevant for only that colour. We assessed how well participants learned all possible target locations (accuracy), how routine was the order of door selections across trials (stereotypy), and how well participants learned to segregate task-routines (setting-accuracy). Overall, L-Dopa had a negligible impact on accuracy, but clearly reduced both stereotypy and setting-accuracy. In the case of accuracy and stereotypy, trait mindfulness modulated the impact of L-Dopa; high trait mindfulness corresponded to increased accuracy and decreased stereotypy, for L-Dopa relative to placebo, whereas low trait mindfulness was associated with the opposite pattern. These results quantify, for the first time, that increasing systemic dopamine availability induces a trade-off between accuracy and stereotypy that is modulated by trait-mindfulness, and that increased dopamine availability increases routine confusion. These findings carry implications for our theoretical understanding of how the brain establishes and switches between task-relevant behavioural routines, which we outline below.

The current findings offer insight into the relationship between dopamine and mindfulness. Dopamine and mindfulness have been indirectly related in both the RL [Kirk et al. (2014); kirkMindfulnessMeditationModulates2015; Kirk et al. (2019)] and active inference frameworks (Friston et al. 2012; FitzGerald, Dolan, and Friston 2015; Laukkonen and Slagter 2021; Giommi et al. 2023), yet there exists no other study to-date that assesses their joint impact on behaviour. Here we find that L-Dopa and mindfulness jointly modulate learning and stereotypy, with L-Dopa yielding conditions of decreased accuracy and increased stereotypy in low trait mindfulness scorers. We hypothesise that low mindfulness results in poorer sensory-action representations which renders the individual more susceptible to error during credit assignment, which is compounded by over-optimistic crediting induced by elevated dopamine availability. The result is a failure to differentiate between the actions that do and do not lead to reward, and an increased probability of reliance on past behaviours. This could be manifest via impoverished top-down, cortical regulation of positive prediction errors in striatum (Kirk et al. 2014), as has been predicted within an RL framework. The same result could also be accounted for by a decrease in certainty regarding sensory prediction errors occurring with low mindfulness (Laukkonen and Slagter 2021; Giommi et al. 2023), in tandem with dopamine inducing inflated certainty regarding reward outcomes (FitzGerald, Dolan, and Friston 2015), as has been suggested via the active inference framework.

Note that the two accounts predict comparable outcomes so we are unable to differentiate between them with the current data. However, the current findings do constrain these accounts regarding the extent of overlap between the actions of dopamine availability and mindfulness. Increased dopamine availability increased routine confusion, regardless of trait mindfulness. Therefore, there are limitations to the modulatory influence of mindfulness on the actions of dopamine. The establishment and maintenance of a task-set is assumed to reflect a superordinate representation of a goal and the set of actions required to attain that goal (Schumacher and Hazeltine 2016; Desrochers et al. 2016; Sutton and Barto 2018; Vaidya et al. 2021; Lee, Hazeltine, and Jiang 2022). The current data suggest that while dopamine and trait mindfulness can jointly modulate the learning and execution of subordinate representations, i.e. the set of actions used, mindfulness does not modulate the impact of dopamine on superordinate task representations, at least under the current task conditions. Future work should determine whether these observed limits in the modulatory influence of mindfulness are due to a limited locus of effect, or are due to increased vulnerability to the impacts of dopamine at superordinate levels of representation.

The finding that L-Dopa increased routine confusion suggests that dopamine modulates switching between tasks requiring multiple responses, as well as between experimentally constrained sensorimotor tasks as has been shown previously (Cools et al. 2001; Mehta et al. 2004; Wiecki and Frank 2010). Collectively, these findings point to a U-shaped function linking dopamine levels and task-switching impairments, in that depleted and inflated levels of dopamine result in greater task-switching deficits. This observation

informs theoretical accounts of the relationship between dopamine and an agent's ability to infer the current task state, which have previously only considered the impacts of depleted dopamine (Friston et al. 2012). However, as the currently studied behaviours are more complex than the constrained sensorimotor tasks that are typically used in task-switching studies, future work should verify whether L-Dopa administration comparably impacts task-switching in simple sensorimotor tasks, and whether depleted dopamine impacts switching between tasks requiring multiple responses. This will determine whether the relationship between dopamine and task-switching is comparable across tasks or is task dependent.

To minimise routine confusion, an agent must maintain a representation of the actions required to achieve the task goal, and must associate this representation to the correct task cues. We found that L-Dopa consistently increased the probability that actions from a non-relevant task-set would be selected during current task performance, whereas the probability that an erroneous action was selected varied across individuals. Therefore, the most consistent locus of task-set confusion is between actions that have been credited as successful in either task-context. What remains to be determined is whether L-Dopa caused task-interference, or whether L-Dopa attenuates the ability to associate successful actions with the appropriate situational cues. If the latter is true, then L-Dopa would have caused individuals to learn one task, that did not incorporate the colour cue as a relevant disambiguating signal. We seek to arbitrate between these possibilities in future work.

In contrast to expectations, L-Dopa lead to an overall reduction in stereotypy in door selections, suggesting that increased dopamine availability reduces the probability of forming a routine when performing multiple responses. This is in contrast to previous findings showing that increased dopamine speeds the transition to habit formation (Harmer and Phillips 1998; Nelson and Killcross 2006; Nadel et al. 2021, 2021). As with task-switching studies, such findings are largely based on rodent models using tasks comprising one or two stimulus-response associations. Our findings show that in the case of sets of task-relevant saccades, increasing dopamine does not necessarily lead to increased habit formation. Moreover, L-Dopa did not improve accuracy overall, suggesting that our results cannot be solely attributed to L-Dopa increasing model-based control (Wunderlich, Smittenaar, and Dolan 2012; Kroemer et al. 2019; Deserno et al. 2021), or adjusting the balance between exploitation and exploration (Kayser et al. 2015; Chakroun et al. 2020).

What then is the influence of dopamine on the cost/benefit computations that drive routine formation? In accordance with previous work with non-human primates (Desrochers et al. 2010; Desrochers, Amemori, and Graybiel 2015), the current data do suggest that dopamine is a modulator of the computations that drive routines in humans. However, the current data also show that the modulatory influence of dopamine is dependent on the behaviour-trait state of the individual. Specifically, increased dopamine appears to drive individuals low in mindfulness towards a stereotypical solution that is suboptimal in terms of accuracy, suggesting a poor evaluation of sequence costs relative to benefits. In contrast, individuals high in trait mindfulness show increased accuracy but reduced stereotypy, suggesting an appropriate crediting of successful actions, but also suggesting some volatility in their execution. While the current data demonstrate the applicability of dopamine signalling to the computations that underlie the formation of routines, the data also show further work is required to determine the internal state variables that determine whether increased dopamine availability will have a positive or negative impact on performance.

The current work is not without limitations. A difference was found in mean BVP between the L-Dopa and placebo sessions, suggesting more general physiological differences between the sessions. However, participants were not able to detect whether they had received L-Dopa or placebo above what would be expected by chance. Therefore, the physiological changes appeared to not be subjectively detectable, lowering the likelihood that they impacted the results. Note that although the power of our blinding test was lowered owing to missing data, the remaining N was comparable to sample sizes from previous investigations into the impact of dopaminergic pharmacological intervention on decision-making, that employed comparable blinding tests (Leow et al. 2023; Pine et al. 2010; Wunderlich, Smittenaar, and Dolan 2012).

Although accuracy and stereotypy theoretically need not be correlated, we did find a moderate positive correlation between the two measures. Critically, the modulatory influence of mindfulness and dopamine on stereotypy was found to be larger after accounting for accuracy. Furthermore, accuracy and stereotypy were at antithesis to each other with regard to the demonstrated impacts of mindfulness and L-Dopa. Nonetheless, further work should be done to confirm the dissociable impact of dopamine and mindfulness on these two aspects of performance. We shall seek to achieve this in future studies by controlling task parameters to maintain accuracy, while examining modulations to stereotypy.

We sought to determine the modulatory influence of dopamine availability and trait-mindfulness on the formation and deployment of task-relevant saccadic routines. We found evidence for theoretical assertions

that dopamine and mindfulness share overlap in their locus of influence, but also demonstrated boundaries in that overlap. Mindfulness modulated the impact of dopamine on task-learning and routine development, with low mindfulness individuals being more likely to demonstrate impaired learning and increased stereotypy during task performance. Invariant to trait-mindfulness, L-Dopa increased the likelihood of confusion between task settings, suggesting that dopamine either hampers the binding of actions to situational cues, or promotes confusion between task-states. Collectively, these data suggest that the fidelity of situational representations interact with reinforcement learning systems to drive the formation of behavioural routines.

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