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Deciding how to Decide: Dopaminergic Mechanisms of Meta Decision-Making

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MSc Thesis

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Abstract

To successfully navigate life, it is crucial not only to make the right decisions but also to determine how much time and effort you want to invest into the decision process itself. Previously, it has been shown that the average reward available in the environment influences cognitive effort exertion and the neurotransmitter dopamine has been proposed as a neural candidate for encoding this average reward rate. In the present study, we investigated the effects of an average reward rate manipulation on cognitive effort in a novel, self-paced perceptual decision-making task in two independent samples ($N_{behavioural}$ = 30, $N_{pharmacology}$ = 46). The role of dopamine in these processes was assessed in a within-subject, double-blind design using the dopamine D2 receptor antagonist sulpiride in the pharmacological sample. In both samples, a high average reward rate led to cognitive effort withdrawal, whereas physical vigour increased with average reward rate in the pharmacology sample. Participants showed different strategies for the task, resulting in large variations in completed trials and possible bonus. In addition, hypothesised results for sulpiride administration are discussed. The findings support the role of the environmental reward rate in the meta-decision of exerting versus withdrawing cognitive effort.

Keywords: cognitive effort, average reward rate, response vigour, dopamine, sulpiride

Introduction

Making decisions constitutes a major part of our day-to-day lives. We want to make decisions and take actions that lead to the most favourable outcome in each situation. Some decisions have small consequences, whereas others impact our lives significantly, for example choosing which educational program to follow. For every decision, you additionally need to determine how much cognitive resources (or cognitive effort) you want to invest to achieve the good outcomes (Kahneman, 1973). Cognitive effort can be defined as the mediating factor between (a) the availability of resources and task demands and (b) task performance (Shenhav et al., 2017). A certain level of effort is needed in all tasks, but exerting cognitive effort comes at both intrinsic and opportunity costs (Niv et al., 2007). Consequently, the question arises: How do we decide when to exert cognitive effort, or when to withdraw to reduce possible costs?

The process of exerting effort is dependent on the allocation of processing resources to the relevant systems via the central executive, the system deemed responsible for attentional control (Baddeley, 2012). However, the capacities of the central executive are limited (Navon & Gopher, 1979; Baddeley, 2012), which constitutes the intrinsic costs of cognitive effort. Additionally, the meta-decision of cognitive effort exertion also comes with 'opportunity costs of time' (Botvinick & Braver, 2015; Boureau et al., 2015; Niv et al., 2007; Shenhav et al., 2017). If one goal-directed process occupies these resources, they cannot be used in the pursuit of another goal. When confronted with limited capacity and time, we must consider when a task is worth investing effort as we could be earning other rewards with these resources. Taking these factors into account, the question of cognitive effort exertion can be rephrased as a cost-benefit trade-off. As this question necessitates an efficient and heuristic way for a smooth decision-making process, it has been theorized that these costs can be estimated with the average reward rate, which describes the reward available in the environment (Niv et al., 2007). This was first examined in response vigour, where a higher average reward rate was related to faster response time in rodents (Niv et al., 2007) and humans (Guitart-Masip et al., 2011; Beierholm et al., 2013). Therefore, a higher reward environment is connected to invigorating effects on physical effort.

In the interest of finding out what determines which decisions are worth effort allocation, the effects of the average reward rate on cognitive effort in place of physical vigour become interesting. In this framework, the increased costs of a higher average reward are theorized to correspond to a withdrawal of cognitive effort (Boureau et al., 2015). As aforementioned, spending time and resources on one decision in a reward-rich environment is costly since this means forgoing additional rewards which could be obtained otherwise. Recent findings show that when the average reward rate is high, a decrease in choice accuracy occurs in difficult trials in addition to the invigoration of response speed (Otto & Daw, 2019). Specifically, the speed-accuracy trade-off shifts downwards with increasing reward rate, i.e., for the same response time, participants perform less accurately when the average reward rate is high. Otto and Daw (2019) conclude that the effects of average reward rate on choice accuracy cannot be fully explained by simply invigorated responses and thus interpreted this pattern as the withdrawal of cognitive effort. This effect was found both in a perceptual decision-making task as well as a cognitive control task (Otto & Daw, 2019). Another study using EEG on the same cognitive control task replicates these behavioural findings and demonstrates that a higher average reward rate is associated with reduced midfrontal theta power (Lin et al., 2022). As midfrontal theta power has been linked to cognitive control, the observed reduction in activity further supports the claim of a withdrawal of cognitive control as a function of reward rate (Lin et al., 2022). Taken together, when the average reward rate is high, physical effort investment goes up, increase response speed and reducing the opportunity costs of time. At the same time, cognitive effort goes down and the probability of errors increases. Concludingly, the evidence suggests that the average reward does indeed serve as a heuristic to determine the cost-benefit trade-off, which in turn governs the physical and cognitive effort that is recruited.

As a basis of the average reward rate, there needs to be a viable and fast neural implication for efficient tracking of these fluctuations in the environment. The neurotransmitter dopamine has been proposed as a neural candidate for encoding the average reward rate (Niv et al., 2005; Niv et al., 2007). Dopaminergic actions are linked to the activation of mechanisms that allow an individual to employ cognitive effort, which in turn prepares behaviour that can result in a reward. Specifically, striatal dopamine depletion in rodents resulted in a reduction of effortful

behaviour (Salamone, Correa, Farrar & Mingote, 2007). In humans, increasing dopamine levels through drug manipulation led to an increased willingness to exert cognitive effort for individuals with a higher dopamine synthesis capacity in the striatum (Westbrook et al., 2020). This is in line with the theory that different aspects of dopamine signalling play a role in guiding action selection (Niv et al., 2007). In reinforcement learning, phasic dopamine signalling in form of reward prediction errors is crucial for learning about previous rewards and predicting future rewards (Montague et al., 1996). Over the course of a task, the accumulation of dopamine caused by the phasic signalling of rewards is observed outside the synaptic cleft, which could be indicative of the average reward rate signalling (Niv et al., 2007). However, since the average reward rate is proposed to serve as a heuristic and predictive decision-making strategy, Niv et al. (2007) suggest that it is unlikely that the average reward rate is simply represented by the result of previous reward signals. They propose that the average reward rate is encoded by the interaction of phasic and tonic dopamine signalling in the striatum. Their computational model of behaviour guided by the average reward rate predicts the effects of tonic dopamine manipulation on response vigour observed in previous work (for a review see Salamone & Correa, 2012). Specifically, the behaviour simulated by reducing the average reward rate predictor in the model mimics the behavioural slowing shown in rats after the depletion of striatal dopamine levels (Niv et al., 2007). Taken together, the framework indeed suggests that the average reward rate is operationalised by the dopaminergic system, with a focus on tonic dopamine release in the striatum.

Previous work shows that increasing overall dopamine levels leads to an enhanced effect of average reward rate. This is indicative by a more pronounced reduction of vigour following administration of the dopamine precursor levodopa when the reward rate was high, compared to the placebo group (Beierholm et al., 2013). Additionally, the availability of ventral dopamine receptors influences the effect of the average reward rate on response vigour (Hird et al., 2022). The question which remains is how dopamine is involved in the effect of the average reward rate on cognitive effort rather than physical vigour. Therefore, in the current project, we investigated the effects of a dopaminergic intervention on cognitive effort investment as a function of reward rate. The aim of the project was two-fold: Firstly, we set out to conceptually

replicate the effect of a fluctuating average reward rate on cognitive effort investment reported by Otto and Daw (2019) using a novel, self-paced perceptual choice paradigm. For this, we adapted a perceptual decision-making task by Oud et al. (2016) with varying difficulty levels in addition to modulating the available reward in the same way as Otto and Daw (2019). This was first tested in a purely behavioural sample. Subsequently, we used the same task and examined the influence of dopamine on the effect of reward rate on cognitive effort, targeting striatal dopamine levels with the selective D2 antagonist sulpiride in a within-subject, double-blind, randomized placebo-controlled design.

The effects of sulpiride are primarily localized to the striatum, due to the high density of D2 receptors (Mehta et al., 2003). At low doses, sulpiride enhances dopamine transmission as it binds to dopamine auto receptors which increases presynaptic dopamine release (Chavanon et al., 2013; Serra et al., 1990). It has been previously shown that sulpiride enhances the motivation to employ cognitive effort (Westbrook et al., 2020) and improves rewards/punishment reversal learning (van der Schaaf et al., 2014). Based on the findings by Otto and Daw (2019), we expected that a higher average reward rate would lead to the withdrawal of cognitive effort. Specifically, we predicted that given the same response time, subjects would be less accurate during trials where the average reward rate is high. Furthermore, since striatal dopamine is proposed to encode the average reward rate (Niv et al., 2007), we hypothesised that dopaminergic manipulation interacts with the effects of the average reward rate manipulation.

Methods

Participants

Behavioural sample. Thirty healthy volunteers were recruited using the SONA participation system of Radboud University. The sample consisted of 1 non-binary, 19 female, and 10 male participants with a mean age of 22.9 (*SD* = 3.7). Exclusion criteria included colour-blindness and a history of neurological or psychiatric disorders. Each participant took part in one thirty-minute session and was reimbursed with €7,50 or study participation credits. Additionally,

participants could earn a bonus of up to €2.50 based on their performance (range €1,21 to €1,76, *M* = 1.58, *SD* = .13). All procedures were approved by the Ethics Committee Social Science (ECSS) of Radboud University (ECSW-LT-2021-10-4-87596). Participants gave written consent before participation.

Pharmacological sample. Forty-seven healthy volunteers were recruited using the SONA participation system of Radboud University as well as via advertisements on social media, course homepages, and on the campus of Radboud University, Nijmegen. One participant discontinued their participation before the end of the study due to personal reasons, resulting in the final sample of 31 female and 15 male participants with a mean age of 22.4 (*SD* = 2.8). Exclusion criteria included a history of (relevant) physical or mental illness, pregnancy or breastfeeding, habitual smoking, and hypersensitivity to sulpiride, carbidopa, or entacapone. Subjects were also excluded for the presence of a first-degree family history of schizophrenia, bipolar disorder, sudden death, or arrhythmia. All participants had normal or corrected-to-normal vision and hearing. A detailed list of all exclusion criteria can be found in supplementary material 1A. Each participant took part in one intake session (3h) and two pharmacology sessions (each 6h). Participants were compensated with €146,00 to €170,00, due to changes in participant compensation rates at the research institute. Additionally, participants could earn a bonus of up to €10,00 per session based on their performance. All procedures were approved by the regional research ethics committee (Medisch-Ethische Toetsingscommissie Oost-Nederland; 2020-7199; ABR: NL76159.091.21). All participants gave written consent before participation.

Task Design

The Twinkling Star Task (Figure 1A) is a perceptual decision-making task adapted from Oud and colleagues (2016) in which participants had to indicate which of the two displays on the screen contains more flickering dots (‘stars’). The task was presented using Psychtoolbox-3 for MATLAB. Each trial began with a 1000ms presentation of the stake (i.e., how many points could be earned by a correct response). To ensure a fluctuating reward rate, four fixed reward sequences (from Otto & Daw, 2019; Figure 1B) were randomized across participants (counterbalanced across drug conditions for the pharmacological sample). The next screen showed flickering dots on the left and right sides of the screen, respectively. The total number

of dots was set at 200, but at any one time, only 20% of the 'stars' were 'on', leaving a degree of uncertainty for the participant. The visible stars were updated each frame. Responses were self-paced; the flickering dots were presented until a button press occurred. Subsequently, feedback was presented, either stating that the response was incorrect or displaying the reward earned. There were four difficulty levels with a difference of stars between the displays of 6 (97 vs. 103), 14 (93 vs. 107), 22 (89 vs. 111), and 40 (80 vs 120). To ensure that the difficulty levels were balanced across the experiment, difficulties were presented in blocks of 16 trials (4 of each difficulty level), while the order was randomized within the block. During the task, both choice accuracy (correct response) and reaction times were recorded.

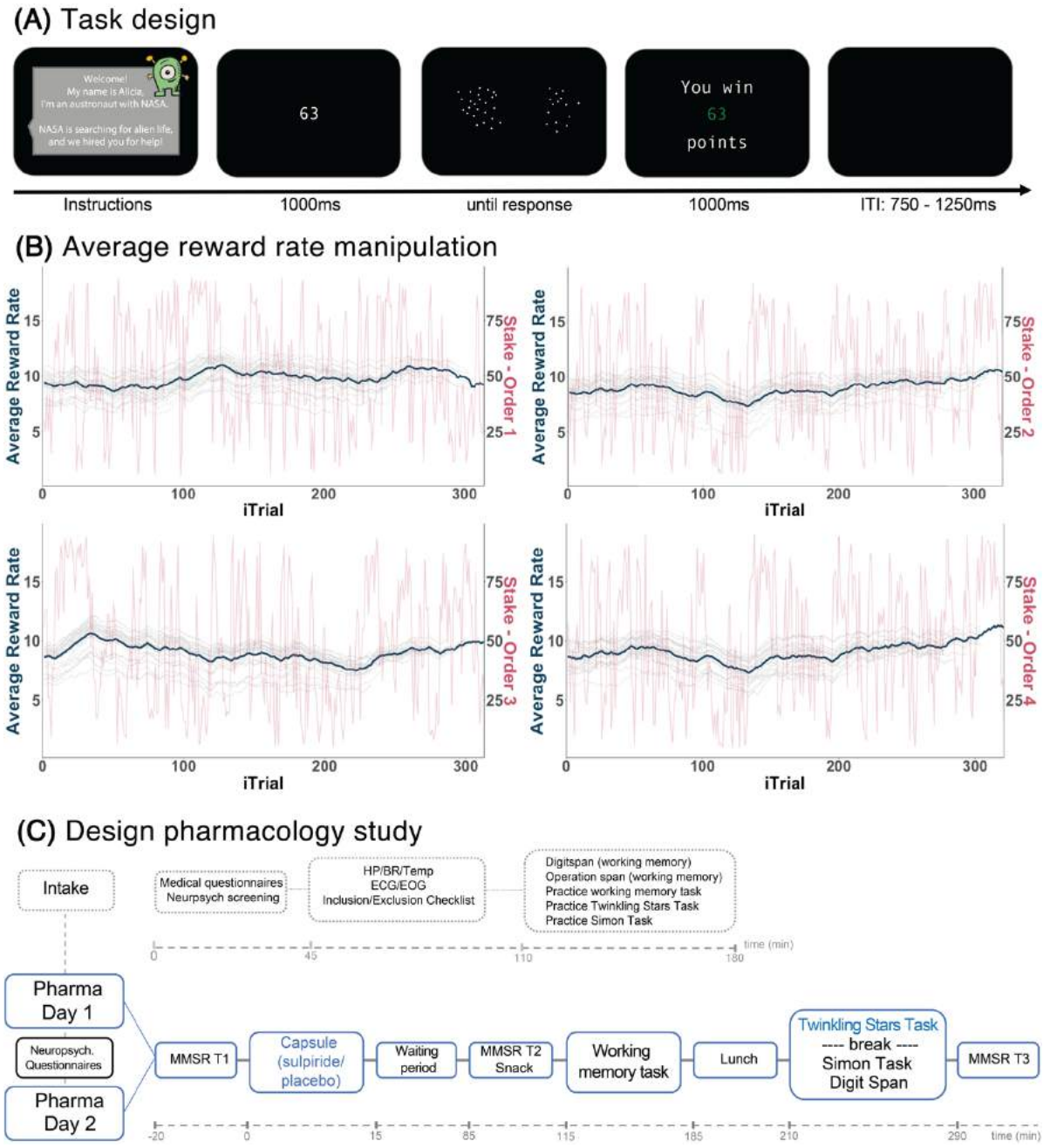

Figure 1: Study design. **(A) Task design.** Example trial in the experimental phase of the Twinkling Stars task. First, stake ("63") was presented for 1000ms. Subsequently, the two displays of stars were presented until a button press occurred. Then, feedback was presented for 1000ms, either indicating a wrong choice ("incorrect"), or, as shown in the figure, the amount that is won. This was followed by a variable inter-trial interval of 750 to 1250ms. **(B) Average reward rate manipulation**. Four different, fixed reward sequences (red) were

pseudo-randomly assigned to participants. The resulting mean (dark blue) and individual (light blue) average reward rates are plotted for each reward sequence. Note that the length of the individual traces depends on the number of trials completed. **(C) Overview Pharmacology study**. Participants took part in one intake and two pharmacology sessions. During the 3h intake session, participants were screened regarding exclusion criteria, performed several baseline measurements, and practiced the main tasks (for an overview see supplementary material 1B). For the pharmacology days, all tasks were performed in a fixed order and time with respect to drug administration. Mood and medical symptom ratings (MMSR) were obtained at three timepoints to monitor drug effects. The procedure for pharmacology day one and two were identical. Additionally, participants completed a battery of neuropsychological questionnaires at home between the two sessions. A description of the complete procedure can be found in supplementary material 1C.

Pharmacological intervention

In the pharmacological sample, a within-subject double-blind randomized-controlled design was employed. Subjects received either sulpiride (400mg Dogmatil, Genzyme Europe B.V.) or a placebo (400mg cellulose) in a counterbalanced order. Sulpiride is a selective D2 antagonist (Farde et al. 1989) and is commonly used in clinical practice for its antidepressant (Rüther et al., 1999) and antipsychotic (Farde et al. 1989) effects. Sulpiride has been approved in the Netherlands and has shown no adverse effects in previous non-clinical intervention studies (van der Schaaf et al., 2014; Westbrook et al., 2020).

General procedure

Behavioural sample. Prior to the start of the task, participants received task instructions embedded in a cover story. They were told that they would help NASA to find alien life by choosing the galaxies with the most stars. Participants were instructed to indicate which side of the screen contained more stars with left and right button presses using a button box. After the instructions, participants practised the task for three minutes to familiarise themselves with the objective. After this practice section, they were informed that the task would now begin and that they could receive points based on correct responses. These points would be then

translated into a monetary bonus of up to €2,50 at the end of the experiment. Participants were informed of the total task duration of 20 minutes and that there would be no trial deadlines. After responding, participants received feedback. Subjects performed the task for 20 minutes without breaks. On average, participants performed 281 trials (*SD* = 36.49) in this timespan.

Pharmacological sample. The data for the pharmacological dataset was collected in the context of a broader study with multiple other tasks (Figure 1C; Supplementary material 1B and 1C). Participants took part in one intake session and two pharmacology sessions. On the pharmacology days, participants received either sulpiride or placebo, followed by a waiting period of 70 minutes, based on previous findings showing that sulpiride plasma concentrations peak around 3 hours after drug intake (Helmy, 2013; Wiesel et al., 1980). In total, participants performed the Twinkling Stars task three times. During the intake sessions, participants practised the task for 10 minutes without receiving points. During the days of the pharmacological intervention, participants performed the task approximately 210 minutes after drug intake. Participants were given an additional 2 minutes of practice before starting the main experiment. The instructions were identical to the behavioural sample. Participants were again instructed that they had 20 minutes to perform as many trials as possible. At the end of the experiment, the total number of points earned was translated into a bonus of up to €5,00 per session. Again, there was no response deadline and participants received feedback after every trial. On average, participants performed 255 trials (*SD* = 33.7) per session. A detailed description of the pharmacological procedure can be found in supplementary material 1C.

Data analysis

All analyses were conducted on trials during the main phase of the experiment. To allow for a 'burn-in' of the reward rate, the first 5 trials were excluded. Outlier trials with RTs outside three standard deviations from the participant's mean within a given difficulty level were changed to the RT ± 3SD for this difficulty level. In line with previous studies (Constantino & Daw, 2015; Otto & Daw, 2019), the average reward rate was estimated in seconds with the following update rule:

$$ARR_{t+1} = (1 - \alpha)^{\tau} ARR_t + (1 - (1 - \alpha)^{\tau}) \frac{r}{\tau}$$

Here, ARR stands for the average reward rate per second, α is the learning rate, τ is elapsed time since the last reward obtained, whereas r stands for the reward obtained. Note that this learning function estimates the reward rate of rewards obtained, not the reward 'available' in terms of the stakes. The learning rate was fixed to 0.0031, i.e., the same as the learning rate used by Otto and Daw (2019). See Figure 1B for the computed ARR traces for each individual.

To assess the effects of average reward rate on physical vigour and cognitive effort, we analysed RT and accuracy respectively. For this, we used mixed-effects regressions in R, with the lmerTest package version 3.1-3; (Kuznetsova et al., 2017), with Satterthwaite's approximation to degrees of freedom for significance estimates. For all analyses, RTs were log-transformed to improve the normality of the distribution. For accuracy, the fixed effect structure of the regression equation was as follows:

$$Correct \sim (ARR + session + logRT) * difficulty + r_{stake} + r_{t-1} + trial + logRT_{mean} + totalScore$$

Here, *session* was included only for the pharmacology sample. Difficulty levels were encoded as a mean-centred linear predictor of four levels (*difficulty*). The reward at stake was denoted by r_{stake}, whereas r_{t-1} was the reward obtained on the previous trial (i.e., the reward for correct responses, and 0 for incorrect responses). Linear trends due to fatigue or training, for example, were captured by the *trial* number. All parametric regressors were z-standardized within-subject (*ARR,* r_{stake}*, trial,* r_{t-1}). All within-subject predictors were included in the full random effects structure. To capture potential between-subject relationships between average response speed and overall score with accuracy, $logRT_{mean}$ and *totalScore* were included as between-subject variables, z-scored across all participants. In this analysis, *logRT* captured the global speed-accuracy trade-off and the interaction of logRT and difficulty examined possible differences depending on difficulty. We expected to see that, having accounted for this trade-off, increased *ARR* would be associated with decreased accuracy, potentially as a function of difficulty level, with the effects more pronounced with higher difficulty levels.

To investigate the effect of ARR on response vigour, a second regression was conducted with logRT as a dependent variable. Again, *session* was only included for the pharmacological sample. To account for the effect of average accuracy on response speed, the mean of accuracy per participant was included ($accuracy_{mean}$):

$$logRT \sim (ARR+session+trial)*difficulty + r_{stake} + r_{t-1} + trial + accuracy_{mean} + totalScore$$

The research question of the relationship between dopamine and average reward rate will be assessed by replacing the *session* variable with *drug* (placebo/sulpiride) in the above-described models. Additionally, the interaction of *ARR* and *drug* will be added.

Results

Basic task effects

Subjects from both samples varied substantially in the number of trials completed. On average, participants from the behavioural sample completed 275 trials (*SD* = 36, range 178-316) in the main phase, slightly less than participants from the pharmacological sample (*M* = 261, *SD* = 34, range 177-314). In both samples, accuracy was above chance level, as determined by the binomial distribution (*Behavioural*: 55% correct based on a one-sided binomial test on 275 average trials; *Pharmacology*: 56% correct based on a one-sided binomial test on 261 average trials). Difficulty level affected accuracy, which was highest in the easiest and lowest in the hardest condition (Figure 2B; *Difficulty*: β_{behav} = -0.77, F_{behav} = 454.4, p_{behav} < .001; β_{pharma} = -0.90 F_{pharma} = 841.6, p_{pharma} < .001). Neither overall accuracy (*Session*: F_{pharma} = 1.8, p_{pharma} = .2) nor the change in accuracy as a function of difficulty (*Session*Difficulty*: F_{pharma} = 0.6, p_{pharma} = .7) was different between sessions in the pharmacology sample (Table 1; right panel). Accuracy decreased with longer RTs (*logRT*: β_{behav} = -0.16, F_{behav} = 0.0, p_{behav} = .002; β_{pharma} = -0.12, F_{pharma} = 4.1, p_{pharma} < .001), but considering the effect of difficulty, the results showed that at higher difficulty levels, spending more time led to increased accuracy (Figure 2C; *logRT*Difficulty*: β_{behav} = 0.13, F_{behav} = 11.3, p_{behav} = < .001; β_{pharma} = 0.07, F_{pharma} = 15.1, p_{pharma} < .001).

RT increased with difficulty in both samples (Figure 2C; *Difficulty*: β_{behav} = 0.08, F_{behav} = 35.5, p_{behav} < .001; β_{pharma} = 0.11, F_{pharma}= 156.6, p_{pharma} < .001). Over the course of the task,

participants significantly sped up in the behavioural (*Trial*: β_{pharma} = -0.04, F_{behav} = 5.7, p_{behav} = .02), but not the pharmacology sample (*Trial*: F_{pharma}= 1.8, p_{pharma} = .2). A reason for this could be the extra training session which the participants in the pharmacology sample received during the intake. Participants from the pharmacology sample were faster during the second session compared to the first (*Session*: β_{pharma} = 0.05, F_{pharma} = 8.7, p_{pharma} = .005). For full statistical reports, see Tables 1 (*Accuracy*) and 2 (*RT*).

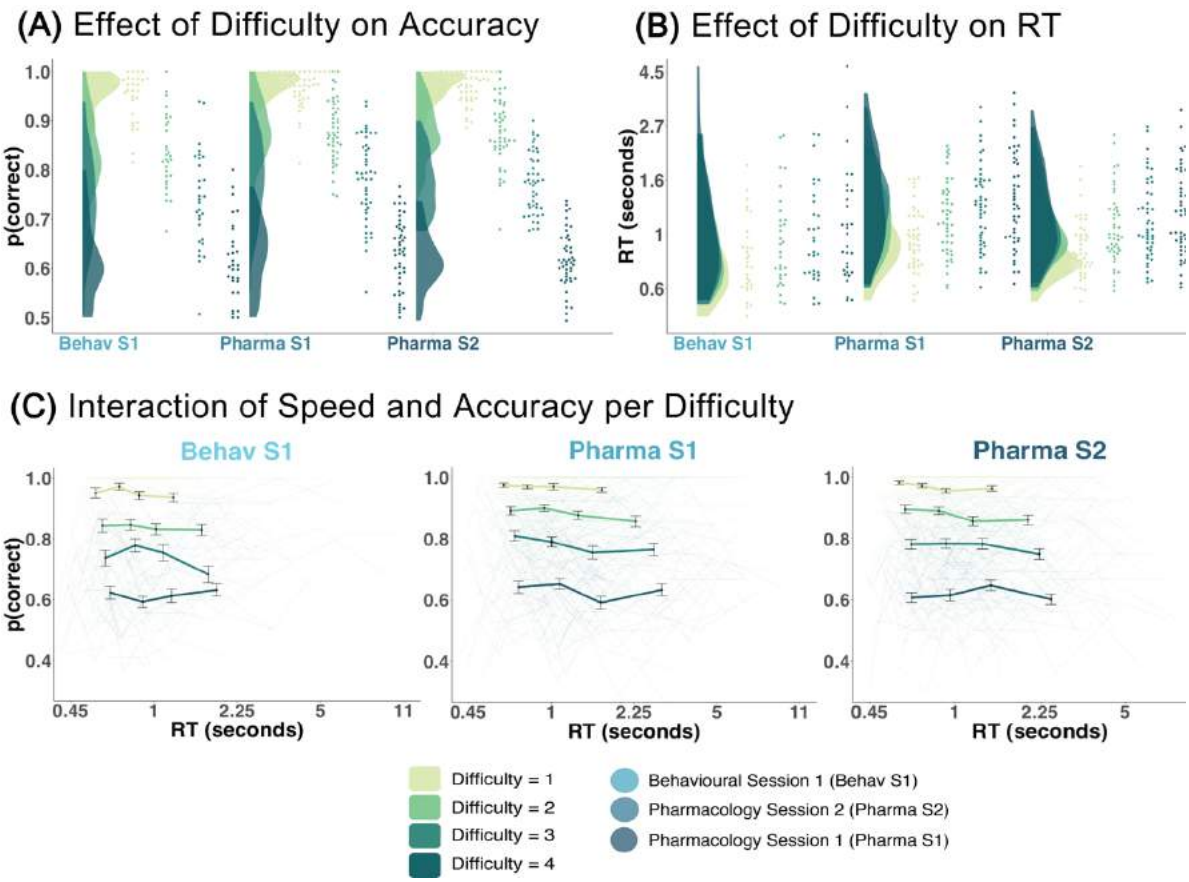

Figure 2: Basic task effects. **(A) Distribution of correct responses for the four difficulty levels**. Participants were more accurate for the easy compared to the hard trials. **(B) Distribution of RT for the four difficulty levels**. Response times increased with difficulty and participants in the pharmacology sample were slower during the second session (left panel). **(C) Interaction of RT and difficulty on accuracy.** Participants were overall less accurate and slower for the difficult trials, but accuracy increased when more time was spent on difficult trials.

Reward affects accuracy

Increasing the average reward rate (ARR) globally decreased accuracy in both samples (Figure 3A; *ARR*: β_{behav} = -0.09, F_{behav} = 3.1, p_{behav} = .02; β_{pharma} = -0.09, F_{pharma} = 36.5, p_{pharma} < .001), suggesting a withdrawal of effort when the average reward rate is high. The effect of average reward rate was not dependent on difficulty level (*ARR*Difficulty*: β_{behav} = -0.03, F_{behav} = 1.8, p_{behav} = .3; β_{pharma} = 0.0, F_{pharma} = 0.0, p_{pharma} = .9). Importantly, the reward obtained on the previous trial did not significantly affect accuracy (*Previous reward*: β_{behav} = 0.06, F_{behav} = 0.4, p_{behav} = .1; β_{pharma} = -0.04, F_{pharma} = 1.3, p_{pharma} = .1), suggesting that the average reward rate effect is not just a downregulation of cognitive effort following a reward. The reward at stake did not affect accuracy in the behavioural sample (*Reward at stake*: F_{behav} = 0.7, p_{behav} = .8), but higher reward at stake increased accuracy in the pharmacology sample (*Reward at stake*: β_{pharma} = 0.06, F_{pharma} = 10.0, p_{pharma} = .01). However, given the different directions of the effect, the effects of the average reward rate are not likely to be a simple function of the reward available. Instead, the average reward effects represent a longer-term integration of past rewards obtained. This shifted the speed-accuracy relationship downwards at a higher average reward rate, such that given the same RT, participants would be less likely to respond accurately under a higher average reward rate.

Reward affects response vigour

The effects of average reward rate on physical vigour (RT) were more complex than for accuracy (Figure 2B). There was a significant decrease in RT with increasing average reward rate in the (larger) pharmacology sample (*ARR*: β_{pharma} = -0.03, F_{pharma} = 22.6, p_{pharma} < .001). The effect was independent of difficulty (*ARR*Difficulty*: F_{pharma} = 0.03, p_{pharma} = .9). In the behavioural sample, there were no significant effects of average reward rate alone (*ARR*: F_{behav} = 0.1, p_{behav} = .7) or in interaction with difficulty (*ARR*Difficulty*: F_{behav} = 2.1, p_{behav} = .2). In contrast to the non-significant effect of stakes on accuracy in the behavioural sample, higher stakes slowed down responding in both samples (*Reward at stake*: β_{behav} = 0.04, F_{behav} = 10.9, p_{behav} = .002; β_{pharma} = 0.03, F_{pharma} = 19.8, p_{pharma} < .001). Again, reward immediately prior did not significantly affect RT (*Previous reward*: F_{behav} = 0.0, p_{behav} = .9; F_{pharma} = 1.1, p_{pharma} = .3), further emphasizing that

effects of average reward rate are driven by integration of past outcomes over a longer time window.

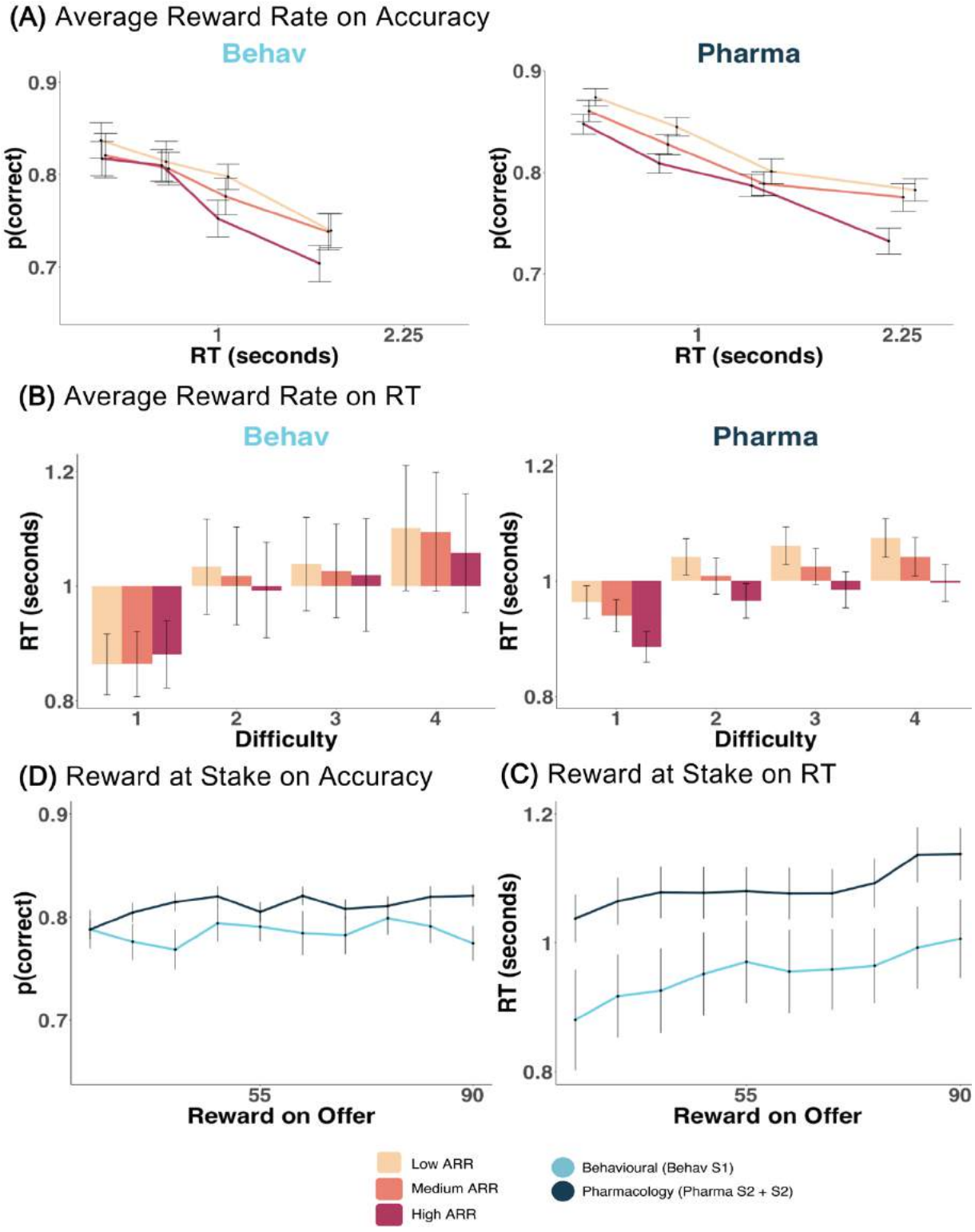

Figure 3: Main effects. **(A) Effect of RT on accuracy for high, medium, and low average reward rate**. We observe a downwards shift of accuracy, meaning that given the same RT, participants are less accurate in both the behavioural sample (left panel) and pharmacology sample (middle and right panel), suggesting a withdrawal of cognitive effort when ARR is high. **(B) Interaction of average reward rate and difficulty on RT**. Higher average reward rate alone led to invigorated response times in both samples. This effect was not dependent on difficulty. **(C) Stake and accuracy**. There is no significant effect of reward on offer in either sample. **(D) Stake and RT**. A higher reward at stake on a given trial is associated with faster RTs. (*Main effects figure per session for the pharmacology sample can be found in supplementary material 2A*)

Individual differences in speed-accuracy trade-off

The self-paced nature of the task combined with the total time limit poses an interesting problem to the participants: They are free to prioritise accuracy by spending a lot of time on individual trials or focus on speed to complete as many trials as possible. Indeed, we observe large individual differences in task performance (i.e., average accuracy) and total score obtained. Across subjects, slower average response time was significantly associated with higher accuracy (Figure 4A*; meanlogRT*: $\beta_{behav} = 0.33$, $F_{behav} = 56.0$, $p_{behav} < .001$; $\beta_{pharma} = 0.30$, $F_{pharma} = 50.1$, $p_{pharma} < .001$). As aforementioned, within-subjects, slower responding was associated with lower accuracy (*logRT*: $\beta_{behav} = -0.16$, $F_{behav} = 0.0$, $p_{behav} < .001$; $\beta_{pharma} = -0.12$, $F_{pharma} = 4.1$, $p_{pharma} < .001$), but accounting for difficulty, slower responding in more difficult trials increased accuracy (*logRT*Difficulty*: $\beta_{behav} = 0.13$, $F_{behav} = 1.8$, $p_{behav} < .001$; $\beta_{pharma} = 0.08$, $F_{pharma} = 15.1$, $p_{pharma} < .001$). Considering the difficulty levels, the magnitude and the direction of response time on accuracy varied between the samples, however, both samples show that longer response times in the highest difficulty led to increased accuracy (*difficulty level 1*: $\beta_{behav} = 0.09$, $F_{behav} = 0.5$, $p_{behav} = .7$; $\beta_{pharma} = -0.08$, $F_{pharma} = 0.3$, $p_{pharma} = .4$; *difficulty level 2*: $\beta_{behav} = 0.08$, $F_{behav} = 2.8$, $p_{behav} = .4$; $\beta_{pharma} = -0.10$, $F_{pharma} = 1.3$, $p_{pharma} = .06$; *difficulty level 3*: $\beta_{behav} = -0.04$, $F_{behav} = 0.0$, $p_{behav} = .6$; $\beta_{pharma} = -0.90$, $F_{pharma} = 2.9$, $p_{pharma} = .05$; *difficulty level 4*: $\beta_{behav} = 0.21$, $F_{behav} = 15.0$, $p_{behav} < .001$; $\beta_{pharma} = 0.0$, $F_{pharma} = 2.5$, $p_{pharma} = .9$). Therefore, slowing down

for higher difficulties is beneficial and subjects who generally respond slower seem to prioritize accuracy.

Concerning task outcomes, slower responding (and thus a lower number of trials completed) across subjects was associated with a lower total score in both samples (Figure 4C*; Total score*$_{RT}$: β_{behav} = -0.21, F_{behav} = 63.7, p_{behav} = < .001; β_{pharma} = -0.19, F_{pharma} = 124.1, p_{pharma} < .001), whereas more accurate responding led to a higher score (*Total score*$_{Accuracy}$: β_{behav} = 0.11, F_{behav} = 5.4, p_{behav} = .02; β_{pharma} = 0.19, F_{pharma} = 30.0, p_{pharma} < .001). The direction of these estimates is not in accordance with the negative correlation shown in Figure 4C. This can be explained by the mediating effect of mean RT on the relationship of mean accuracy on score ($ACME_{behav}$ = -15.9, 95% CI_{behav} [-16.2, -15.6], p_{behav} < .001; $ACME_{pharma}$ = -18.4, 95% CI_{pharma} [-18.7, -18.1], p_{pharma} < .001). Thus, when only considering the effect of accuracy, the results indicate that higher accuracy correlates with lower score (Figure 4B), but with the variability explained by the reduction in RT, the effect was shown to be positive. In conclusion, quicker response time leads to a higher score but with the increasing response speed, choices also need to be accurate to reach a high score.

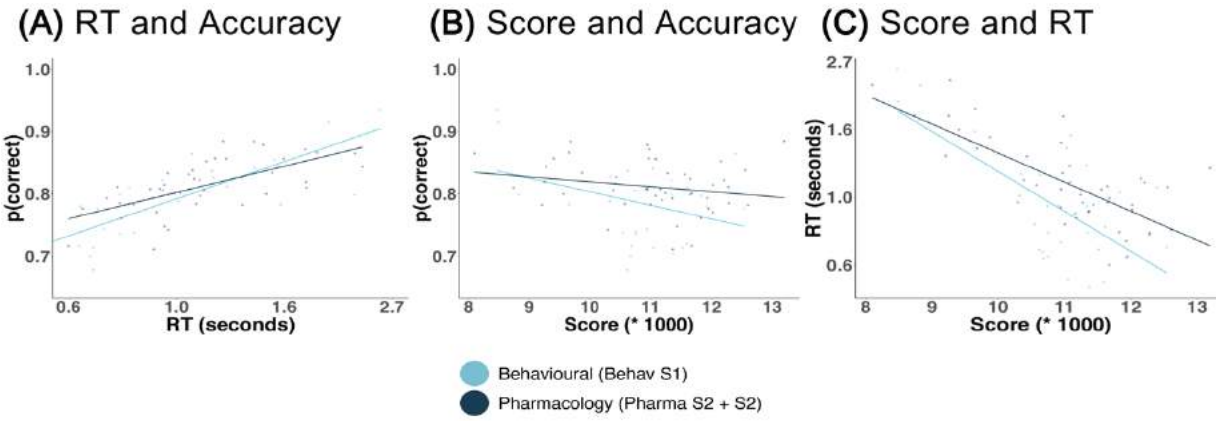

Figure 4: Individual Differences. (**A) Average RT and Accuracy**. Between-subjects higher average RTs are associated with higher accuracy. **(B) Score and accuracy**. Within-subjects, higher accuracy is significantly related to a higher score in both samples, however,

participants with higher mean accuracy receive fewer points overall. **(C) Score and RT**. Faster RTs are associated with higher score, both within individuals as well as between.

Accuracy

	Behavioral sample					Pharmacology sample				
			CI					CI		
Predictors	*Estimates*	*SE*	*LL*	*UL*	*p*	*Estimates*	*SE*	*LL*	*UL*	*p*
(Intercept)										
ARR	-0.1	0.04	0.84	0.98	**.02**	-0.09	0.02	0.87	0.96	**< .001**
Difficulty	-0.77	0.04	0.43	0.50	**< .001**	-0.90	0.03	0.38	0.43	**< .001**
Previous reward	0.06	0.04	0.99	1.14	.1	-0.04	0.02	0.92	1.01	.1
Reward at stake	-0.01	0.04	0.92	1.06	.8	0.06	0.02	1.02	1.11	**.01**
logRT	-0.16	0.05	0.76	0.94	**.002**	-0.12	0.03	0.84	0.93	**< .001**
Trial	-0.10	0.04	0.85	0.98	**.01**	-0.06	0.02	0.90	0.99	**.01**
ARR * Difficulty	-0.03	0.03	0.91	1.03	.3	0.00	0.02	0.96	1.05	.9
logRT * Difficulty	0.13	0.04	1.06	1.23	**< .001**	0.08	0.02	1.04	1.13	**< .001**
Mean logRT	0.33	0.05	1.28	1.52	**< .001**	0.30	0.04	1.27	1.45	**< .001**
Total score	0.11	0.05	1.02	1.22	**.02**	0.19	0.04	1.13	1.30	**< .001**
Session	-	-	-	-	-	0.04	0.03	0.98	1.10	.2
Session * Difficulty	-	-	-	-	-	-0.01	0.03	0.94	1.04	.7

Table 1. Full statistics for the models on choice accuracy for the behavioural (left) and pharmacology (left) samples.

RT

	Behavioural sample					Pharmacology sample				
			CI					CI		
Predictors	*Estimates*	*SE*	*LL*	*UL*	*p*	*Estimates*	*SE*	*LL*	*UL*	*p*
(Intercept)										
ARR	-0.00	0.01	-0.03	0.02	.7	-0.03	0.00	-0.04	-0.02	**< .001**
Difficulty	0.08	0.01	0.06	0.11	**< .001**	0.11	0.01	0.10	0.13	**< .001**
Previous reward	0.00	0.01	-0.01	0.01	.9	0.00	0.01	-0.00	0.02	.3
Reward at stake	0.04	0.01	0.01	0.06	**.002**	0.03	0.01	-0.00	0.02	**< .001**
Trial	-0.04	0.02	-0.07	-0.01	**.02**	-0.01	0.01	-0.03	0.01	.2
ARR * Difficulty	-0.01	0.00	-0.02	0.00	.2	0.00	0.00	-0.01	0.01	.9
Trial * Difficulty	-0.00	0.00	-0.01	0.01	.8	-0.00	0.00	-0.01	0.00	.09
Mean Accuracy	5.10	0.46	4.19	6.01	**< .001**	3.89	0.43	3.03	4.74	**< .001**
Total score	-0.21	0.03	-0.26	-0.16	**< .001**	-0.19	0.02	-0.22	-0.15	**< .001**
Session	-	-	-	-	-	0.05	0.02	0.02	0.09	**.005**
Session * Difficulty						0.00	0.00	-0.00	0.02	.13

Table 2. Full statistics for the models on response vigour for the behavioural (left) and pharmacology (left) samples.

Hypotheses: Dopamine and average reward rate

The final analyses of this study, which have not yet been possible given that the data remains blinded as data collection has not yet been finalized, will concern the effects of administration of the D2 receptor blocker sulpiride. Here, we will present our hypotheses regarding the effects of sulpiride mediating the effects of reward rate on cognitive effort. Depending on whether the administered dose of sulpiride acts predominantly on the presynaptic or postsynaptic neuron, we hypothesise effects in opposite directions. Low doses of sulpiride have been linked to antagonistic actions on D2 auto receptors at the presynaptic neuron (Chavanon et al., 2013; Serra et al., 1990). In this case, synaptic dopamine release is disinhibited, as activation of these auto receptors is linked to inhibitory effects on voltage-dependent activation of local channels, leading to a suppression of dopamine release (Ford, 2014). If the average reward rate is indeed encoded by dopaminergic transmission (Augustin et al., 2020), the increase in synaptic dopamine would result in the average reward rate being encoded as higher and thus cause cognitive effort withdrawal. Here, two mechanisms are possible: The withdrawal of cognitive effort affects all conditions equally, evident by decreased accuracy at the same RT during all reward environments in the same magnitude (Figure 5A, left panel). Or, if cognitive effort is already low in the high reward environments, then this effect might be evident only in the low and medium reward environments, shifting performance down more selectively (Figure 5A, right panel).

However, if sulpiride acts primarily at the postsynaptic D2 channels, effects in the opposite directions are expected. Postsynaptic D2 antagonism is expected to reduce post-synaptic sensitivity to dopamine, leading to lower postsynaptic activity. This would then result in the average reward rate being encoded as lower (Figure 5B), leading to more cognitive effort exertion in general, evident by higher accuracy at the same RT for all reward rates (Figure 5B, left panel), or inhibiting the reduction in cognitive effort in the high and medium reward environments selectively (Figure 5B, right panel).

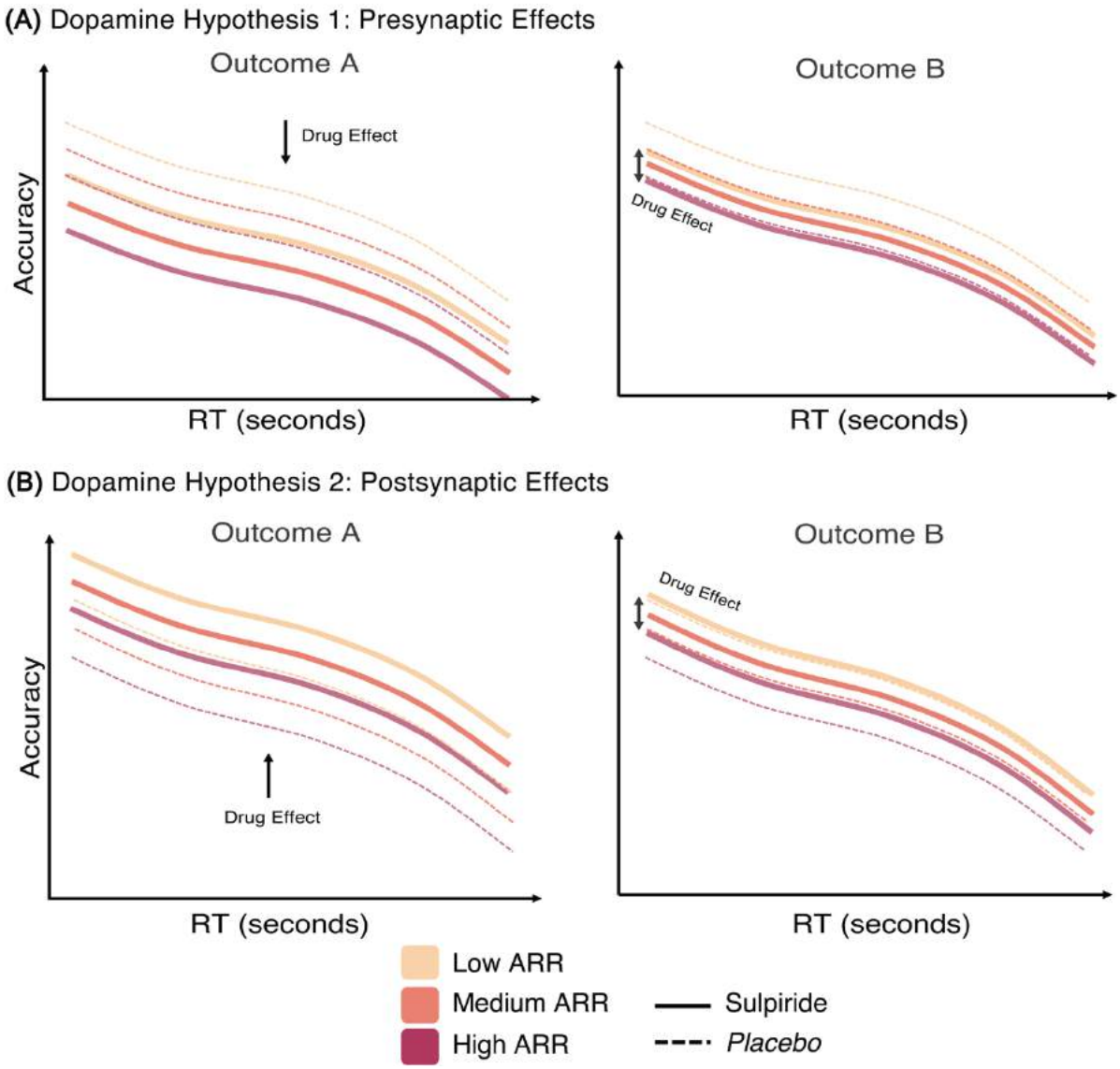

Figure 5: Drug manipulation. **(A)** *Left panel*: General decrease in cognitive effort; *Right panel*; Reward rate specific decrease in cognitive effort; **(B)** *Left panel:* General increase in cognitive effort; *Right panel*; Reward rate specific increase in cognitive effort

Discussion

The present study examined factors that shape the meta-decision of how much cognitive effort to invest in a decision. Specifically, we investigated the role and neural basis of the average reward rate as a heuristic to determine cognitive effort exertion. In a simple perceptual decision-making task with an overall time limit, but without a trial-wise response deadline, we found that a higher average reward rate was associated with a decrease in cognitive effort, while response vigour was increased. We then replicated and extended these findings in a psychopharmacological study using the selective D2 antagonist sulpiride in a within-subject, double-blind procedure to examine the role of dopamine as a putative neural basis of reward rate encoding. Here, we hypothesise that modulation of dopamine transmission interacts with the effect of the average reward rate. Finally, we observed strong inter-individual variability in how participants approached this task, showing that participants varied to the degree to which they would slow down to increase accuracy, at the cost of a lower number of trials they could complete.

Average reward rate modulates cognitive effort and vigour

In the process of meta-decision making, effort exertion is both relevant in the physical (concerning response vigour) as well as in the mental domain (referring to cognitive effort). The theoretical framework suggests that the opportunity costs of time increase when reward in the environment is plentiful, thus invigorating responses (Niv et al., 2007). Following this view, the average reward rate is also proposed to modulate cognitive effort. When there are plenty of opportunities to earn rewards, individuals are less willing to put the time and resources (i.e., effort) into a single decision process (Shenhav et al., 2017). In our novel task design, we found robust effects on accuracy across both samples, following a similar pattern as reported by Otto and Daw (2019). Accuracy decreased as a function of the average reward rate. Importantly a higher reward rate shifted the relationship between accuracy and RT, such that given the same response speed, participants would respond less accurately under higher reward rates. Thus, the effect on accuracy cannot be explained by reduced time allocation only. Crucially, this finding was not a simple Gratton-like effect, i.e., upregulating cognitive effort following the

action of the previous trial, as there was no effect of the previous reward obtained (Gratton et al., 1992). Rather, the effects are due to the integration of rewards on a longer timescale, suggesting that the average reward rate indeed does serve as a metric to determine cognitive effort investment.

A higher average reward rate was related to enhanced response speed in the (larger) pharmacological sample, as previously reported in different paradigms (Beierholm et al., 2013; Guitart-Masip et al., 2011; Hird et al., 2022; Otto & Daw, 2019) and modelled by Niv et al (2007), supporting the idea that reward rate may indeed serve as a heuristic that approximates the opportunity cost of time. However, this effect was not significant in the behavioural sample, which may be due to the smaller sample size. In the pharmacology sample, a clear negative effect of the average reward rate on response time was observed, independent of difficulty. In previous studies using a cognitive control task with congruent and incongruent options, average reward rate effects on accuracy were only found for incongruent (and thus more difficult) trials (*Study 2*: Otto & Daw, 2019; Lin et al., 2022). In the current study, difficulty did not interact with average reward rate, in line with the effects seen in another perceptual decision-making task (*Study 1*: Otto & Daw, 2019), indicating that congruency and perceptual difficulty do not affect these meta decision processes in the same way. Taken together, the present results suggest that the average reward rate serves as an important heuristic to aid in the meta-decision of resource (cognitive effort as well as physical vigour) allocation.

Reward at stake modulates physical vigour and cognitive effort

As opposed to the previous work regarding the effect of reward at stake on accuracy (Lin et al., 2022; Otto & Daw, 2019) and most studies on vigour (Beierholm et al., 2013; Guitart-Masip et al., 2011), there was a significant effect of reward at stake on vigour in both samples and on accuracy in the pharmacology dataset. In contrast to the effect of average reward rate (which reduced accuracy), a higher reward at stake *increased* accuracy. Against our hypothesis, reward at stake significantly affected response time in both samples, slowing down responding when a higher reward was at stake. Although not significant in the majority of studies assessing the effect of reward at stake while correcting for average reward rate, the direction of this effect is in line with previous studies (Beierholm et al., 2013; Guitart-Masip et al. 2011; Otto & Daw,

2019). Additionally, a recent study by Hird et al. (2022) reports a significant positive relationship between reward at stake and response times, also indicating that subjects responded slower when the reward at stake was higher.

A potential explanation for the effects in the current sample could be that the task we used did not include a trial deadline, allowing participants to adjust their choice strategy. For the pharmacology sample, participants slowed down significantly while accuracy increased when the reward at stake was high This could indicate a shift in strategy to focus on increasing accuracy. In the behavioural sample, participants slowed down when the stakes were high but that did not lead to higher accuracy. Follow-up analyses targeted at the interaction of stake and response time on accuracy could explore this relationship further. Another potential explanation for the significant effects of stake could be reward prediction errors if the reward at stake was different than predicted by the average reward rate. Depending on the directionality of the difference in prediction and actual reward, it is possible that the reward at stake affects accuracy differently than the average reward rate. Again, this relationship could be addressed in future analyses.

Inter-individual differences in decision-strategy

The perceptual decision-making task used in this study required the participants to maximize both accuracy, since no points are awarded for incorrect trials, but also speed, as more trials lead to more points that can be gained. Interestingly, we found that the relationship between accuracy and score is appears negative, initially suggesting that more accurate responses lead to a lower score, an effect that is not supported by the mixed-model analysis. Follow-up mediation analyses revealed that this change in direction can be explained by the mediating effect of RT, so if accounting for the negative relationship between RT and score (meaning that faster responding leads to higher score), accuracy needs to be high as well to reach the favourable outcome of a higher score and thus bonus.

Another unique aspect of the task is the irreducible uncertainty. A consequence of this is that extensive evidence accumulation does not guarantee a correct choice. Especially in harder trials where only four stars differ between the display sides, participants ultimately must guess.

Accordingly, the most beneficial strategy would be to adapt the behaviour over the course of the experiment and respond more quickly to the harder trials as the opportunity costs increase with the duration of evidence accumulation. However, we observe no interaction of trial and difficulty or session and difficulty on response time in neither sample. This suggests that participants do not change their response strategy with regards to speed differentially for the varying difficulties. This might be due to the implicit difficulty manipulation; participants are unaware that there are four different levels and thus perceive the fluctuations as random.

The response pattern in the present study indicated that some individuals appear to prioritize accuracy and spend more time to achieve higher accuracy, to their own detriment, as this happens at the cost of their total monetary bonus. Oud et al. (2016), who developed the Twinkling Stars task, investigated the difference between a response deadline in contrast to self-paced responding without a reward rate manipulation. They suggested that participants behave maladaptively when on trials without a deadline, wasting time on difficult trials that do not provide a large reward (Oud et al., 2016). For future research, it would be interesting to examine the differences in response patterns in deadline trials versus free-response trials with respect to the involvement of the average reward rate. A deadline could possibly stress the increase of subjective opportunity costs across the experiment, as it makes the time spent on a decision explicit. Furthermore, the observed differences between individuals could be due to personality traits, such as perfectionism. Individuals with high perfectionism traits tend to spend extensive time on tasks where the gain is (objectively) not worth the effort (Kağan et al., 2010). A possible negative outcome of such a persistent behavioural pattern can be burnout, which has previously been linked to perfectionism (Hill, & Curran, 2016). Future research could focus on connecting these behavioural patterns to character traits, as this could illuminate which aspects of the decision-making process are possibly linked to maladaptive behaviours.

Caveats and considerations

There was a striking absence of the expected speed-accuracy trade-off within participants. Participants slowed down when higher rewards were at stake and sped up when the average reward rate was high, and similarly became more/less accurate, respectively. Yet, people were overall significantly slower on incorrect trials. This did interact with difficulty, such as that

slower reaction times in more difficult trials were associated with higher accuracy, however, there was no clear linear pattern. This difficulty manipulation in this design could possibly account for the lack of a speed-accuracy trade-off in this study. A likely explanation for this observation is the degree of irreducible uncertainty. As aforementioned, evidence accumulation is only informative up to a certain point. This explains why accuracy moves in the direction of chance level in the difficult trials and drives accuracy down for the higher RT bins in the speed-accuracy trade-off. While the degree of uncertainty in the choice and self-paced responses allow the examination of different response profiles and strategies, this aspect of the task should be considered in the study design.

Hypothesised role of dopamine mediating the effects of average reward rate

The overarching aim of the present study was to test the hypothesis that dopamine mediates the effects of average reward rate on cognitive effort and vigour, putatively through tracking the reward rate. The outcome and direction of the D2 receptor antagonist sulpiride administration in these studies could not yet be determined as data collection was ongoing at the time of writing this thesis, and thus could not be de-blinded. Here, we will briefly discuss the main literature and specific hypotheses. Theory (Niv et al. 2005; Niv et al. 2007) and previous empirical studies (Beierholm et al., 2013; Westbrook et al., 2020) strongly suggest an involvement of the striatal dopaminergic system. The indirect dopaminergic pathway has been found to be involved in regulating response vigour (Augustin et al., 2020). It also has been hypothesised to be involved in cognitive effort, as D2 receptor actions have been linked to higher sensitivity to the cost-benefit trade-off between effort and reward (Collins & Frank, 2014). Further, pharmacological research in rodents indicates that D2 receptors modulate the costs of effortful behaviours via gating the disinhibition of the indirect pathway (Mourra et al., 2020). In humans, boosting dopamine levels pharmacologically has been found to increase the effect of the average reward rate on response vigour (Beierholm et al., 2013) and enhanced willingness to exert cognitive effort, but only in participants with lower dopamine synthesis capacity (Westbrook et al., 2020).

On the basis of this framework, manipulating dopaminergic actions via the D2 receptors is expected to modulate the effects of the average reward rate on cognitive effort. A low dose of

sulpiride has been previously linked to presynaptic effects on D2 auto receptors, leading to increased dopamine levels (Chavanon et al., 2013; Serra et al., 1990). As administration of 400mg sulpiride has been previously used as a low dose (Westbrook et al., 2020), we hypothesise that the reward rate under sulpiride is encoded as being higher, leading to decreased effort (Figure 5A). If a high average reward rate does not lead to maximal dopamine signalling in the relevant pathway, the effect is predicted to be equal during all trials and accuracy should shift down in all reward environments. If effort withdrawal is already maximal in the high reward environment, only lower and medium reward rates are expected to shift down, while a larger effect would be expected for a lower average reward rate. Accordingly, the behaviour of participants under sulpiride could represent reduced accuracy given the same response time across all average reward rates equally, with the highest average reward rate still showing the lowest speed-accuracy trade-off. Or, for the second option, accuracy given the same response time could decrease most for lower and medium average reward rates, causing them to become more like the effect of the high average reward rate on placebo. Alternatively, postsynaptic D2 antagonism is expected to lead to opposite effects, with the average rate being encoded as lower and thus resulting in less cognitive effort withdrawal (Figure 5B).

Using Positron emission tomography (PET), Hird and colleagues (2022) assessed the role of D1 receptors density on the influence of average reward rate on response vigour, reporting that higher D1 density led to longer response times. As this effect was found to be in the opposite as hypothesised direction, they speculated that the invigorating effects of a higher average reward rate might be dependent on D2 receptor actions in the indirect pathway as compared to D1 receptor mechanisms (Augustin et al., 2020; Hird et al., 2022). This further supports the view that the effects on cognitive effort are also dependent on D2 receptors. Thus, investigating the differences in D2 density is an important future target for research. Other studies indicate that the actions of sulpiride on cognition rely on the individuals' dopamine synthesis capacity (Westbrook et al., 2020), which could also play a role in the effects in the pharmacology study. The direction of the effect in the present sample will help to identify the neural underpinnings of these meta-decision processes and provide suggestions for further research directions.

Conclusion

In conclusion, the present study shows that a higher average reward rate led to cognitive effort withdrawal while physical effort was invigorated. Thus, we replicated the effects of average reward rate manipulation reported in previous studies in a novel, self-paced paradigm, with the main effects of interest being consistent across both samples. Furthermore, we observed large individual differences in task strategy, which poses interesting questions for future research. Lastly, the question which remains is the role of dopaminergic processes involved in the effect of average reward rate, which will be examined in the near future.

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Supplementary material

Contents

Supplementary material 1 – Details pharmacology study

Supplementary material 1 A – Inclusion/Exclusion list

- Do you have any mental objects in or around your body?
- Are you claustrophobic?
- Do you have abnormal hearing?
- Do you have uncorrected vision?
- Do you use:
    - More than 3 alcohol beverages daily?
    - Psychotropic medication or recreational drugs weekly?
    - Cannabis weekly or more?
    - More than one package of cigarettes weekly?
- Are you unable to stop using:
    - Psychotropic medication or recreational drugs (over a period of 72 hours before testing)?
    - Alcohol (over a period of 24 hours before testing)?
    - Smoking (over a period of 24 hours before testing)?
- Do you have a history of clinically relevant:
    - Psychiatric disease
    - Neurological disease
    - Endocrine/ metabolic disease
        - Do you sweat a lot? (covers Cushings)
        - Do you drink more than 3L fluid a day? (covers Cushings)
    - Obstructive respiratory disease, such as astma or COPD
    - Hepatic/ cardiac/ renal disease (hepatic = liver, renal = kidney)
    - Heart related disease
    - Cerebrovascular/ metabolic/ pulmonary disease
    - Epilepsy
    - Drug dependency (opiate, LSD, (meth)amphetamine, cocaine, solvents, or barbiturate)
    - Alcohol dependence
    - Reynaud's syndrome
        - Do you have problems with your fingers or toes when there is cold weather, or at temperature changes (numbing, discoloring)?
    - Glaucoma
        - Do you have problems with visual field loss or increased eye ball pressure?
    - Diabetes
- Are you currently being treated for a clinically relevant
    - Chronic disease
    - Hypo/ hypertension
    - Renal failure
    - Hyperthyroidism

    - Acute inflammatory disease
    - Peptic or duodenal ulcers
    - Glaucoma
- In the week prior to the start of the study did you use:
    - Corticosteroids?
        - Such as prednisolone, or a strong cream for eczema
    - MAO inhibitors?
    - Antidepressants?
        - Such as Prozac, efexor, or citalopram
    - Antipsychotics?
        - Such as Seroquel, zyprexia, Haldol or clozapine/leponex
    - Anesthetics?
- Are you oversensitive to sulpiride, carbidopa or entacapone?
- Do you have a history of:
    - Prescribed medications within the last month? (exception: regular use of contraceptive medication)
    - 'Over the counter' medication within the last 2 months (exception: occasional use of paracetamol, acetylsalicylic acid, and ibuprofen)
    - Regular use of corticosteroids?
        - E.g. for an allergy (food allergies, hay fever)
        - Such as prednisolone, or a strong cream for eczema
- Doe you have (a history of) frequent autonomic failure?
- Do you have epilepsy?
- Do your parents or siblings have health problems?
- Do you have a family history of sudden death or ventricular arrhythmia or other heart problems?
- Do you have a first-order family history of schizophrenia, bipolar disorder or major depressive disorder?
- Do you have an irregular sleep/wake rhythm?
- Do you carry out daily intense physical exercise?
- Do you have current parodontitis?
- If female:
    - Are you pregnant or breastfeeding?
    - Are you using appropriate contraception?
    - Are you planning to continue using your contraceptive for the coming months?
    - Do you have the intention to stop using your contraceptive in the near future?

Supplementary material 1 B – All tasks and measurements

Tasks

- Simon task (drug parameter; behavioural)
- Twinkling Stars task (drug parameter; behavioural)
- Working memory gating task (drug parameter; behavioural and fMRI)
- Eye blink rate (baseline parameter)
- Operation span (baseline parameter)
- Digit span test (baseline and drug parameter)

Questionnaires

- Beck Depression Inventory (BDI; baseline)
- Barratt Impulsiveness Scale (BIS-11; baseline)
- BIS/BAS Scale (Behavioural inhibition scale/Behavioural activation scale; baseline)
- STAI (State and Trait anxiety inventory; baseline)
- Utrechtse Burnout Schaal (UBOS; baseline)
- Covid-19 stress scales (CSS; baseline)

Medical measures

- Height (for screening purposes)
- Weight (for screening purposes)
- Blood pressure (for screening purposes and drug effects)
- Body temperature (for screening purposes and drug effects)
- Pulse (for screening purposes and drug effects)
- Electrocardiography (ECG, for screening purposes)
- Respiration (during MRI scanning)
- Alcohol use (for screening purposes)
- Nicotine use (for screening purposes)
- Drug use (for screening purposes)
- History of mental and physical health (for screening purposes)
- Subjective self-report measurements (for drug effects)
- Menstrual cycle stage (for drug effects in female participants)

Supplementary material 1 C – fMRI-pharmaco procedure

The broader study was designed to investigate the effects of dopaminergic manipulation on multiple aspects of cognition, including working memory, cognitive control, and effort allocation during decision-making. Of the total sample, 38 (23 women) participated in the pharmaco-fMRI part of the study, the remaining 8 participants (8 women) performed all tasks outside the scanner. Apart from the absence of the scanning, the procedure stayed the same. Each participant took part in four sessions: a phone screening, a 3-hour intake session, and two 5.5-hour pharmacology sessions. During the pharmacology sessions, the order of the drugs was counterbalanced and blind to both participant and experimenter.

Participants were recruited around Radboud University campus using posters and advertisements on course websites and the Radboud University research participant system (SONA system) and via social media. After sign-up, participants were sent an information brochure (supplementary material 1D), including information about the study procedure, information about the drug sulpiride, and a list of exclusion criteria. Participants were given at least one week to review the material and determine eligibility and interest in the study. They were then called by a member of the research team to review the exclusion criteria and answer potential questions. If participants are eligible based on the phone screening, they were invited for a center screening.

During this screening procedure at the research center, participants first gave written consent and subsequently underwent a medical and psychiatric screening procedure. Measures included height, weight, blood pressure, body temperature, heart rate, electrocardiography, personal and family history of relevant medical and psychiatric conditions, neuropsychological status, and presence of (relevant) DSM-IV disorders. A comprehensive list of exclusion criteria can be found in supplementary material A. Participants also completed a battery of baseline measurements, including working memory capacity (digit span and operation span) and spontaneous eye-blink rate using electrooculography. Finally, participants practiced the three tasks of interest. The measures were then reviewed by a medical doctor who determined if the participant could be included in the main part of the study.

For the pharmacology sessions, participants were instructed to refrain from using cannabis 14 days before each session, psychotropic medication or recreational drugs 72h before each session, drinking alcohol 24h before each session, and smoking or drinking stimulant-containing beverages the day of the session. The session started with a screening form, a pregnancy test for female participants, baseline subjective measures regarding affect and mood, and baseline physical measures including heart rate, blood pressure, and temperature. The subjective and physical measures were repeated at two additional time points during the day to monitor drug effects. Participants then received either 400mg of sulpiride or placebo in a counterbalanced order. This was followed by a 70-minute waiting period to allow the drug to reach peak effect, as established by previous studies (Mehta et al., 2004; Mehta et al., 2003; Mehta et al., 2008). For the pharmaco-fMRI part of the project, the participants were then prepared for the measurement with a Siemens MAGNETOM Skyra 3 Tesla MR scanner located at the Donders Institute of Neuroimaging, Nijmegen. A high-resolution anatomical scan was acquired, followed by four 15-minutes blocks of a working memory gating task. For the non-fMRI part of the project, this task was performed on the computer outside of the scanner. Afterward, participants were offered lunch. Participants then performed two computerized tasks for approximately 30-minutes each, one of which was the Twinkling Stars Task. Lastly, the participant's fitness to travel was assessed to ensure that they can safely leave by foot or public transport. Participants were asked to refrain from biking and driving for a subsequent 24 hours.

Both pharmacology sessions were identical in content and timing, with the only difference being the compound. The span between the two pharmacology days was kept as consistent as possible, with at least one week and at most 2 months in between. Between the pharmacology sessions, participants were sent multiple questionnaires to be filled out at home. These included measures of depressive symptoms, state/trait anxiety, behavioural inhibition/activation, burn-out symptoms, impulsivity, and Covid-19 related stress. The complete list of tasks and measurements can be found in supplementary material 1B.

Supplementary material 1 D – Participant Information

INFORMATION FOR PARTICIPANTS IN THE STUDY:
"DOPAMINE AND COGNITION"

Dear participant,

In this brochure, you will find all the information you need in order to decide whether you wouldlike to participate in the study "Dopamine and Cognition". All procedures are described in detailbelow. Please read the following information carefully before deciding whether to participate in this study. In the appendices you will find:

- Information leaflets about the medication used in this study
- Medical checklist to determine whether you can be invited for an intake appointment.
- Information about the insurance for participants
- A copy of the consent form that you must sign before you can participate in this study.

WHY ARE WE DOING THIS RESEARCH?

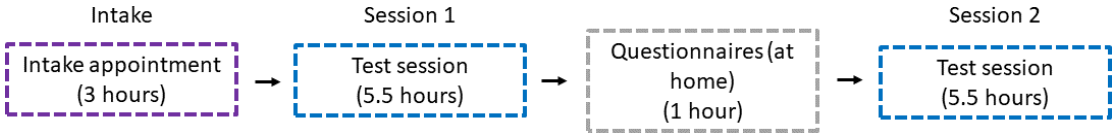
This research focuses on the link between dopamine and brain function. Dopamine is a brain chemical that affects a number of cognitive processes, including decision-making, learning, working memory, and motivation. Too much or too little dopamine, as is the case in schizophrenia and Parkinson's disease, for example, can lead to changes in decision-making and how you respond to rewards. The aim of this study is to understand how changes in brain dopamine affect memory, learning, and decision making. To achieve this goal, we will administer a drug that mimics dopamine's effects in the brain (sulpiride, brand name Dogmatil) and a placebo (a dummy pill with no active ingredient).

Sulpiride is prescribed for, among other things, in higher doses, the treatment of psychoses and/or schizophrenia. Our lab has safely used this low dose of sulpiride in several previous studies. At the low dose we will use in the current study, we do not expect you to experience any strong side effects of the drug, nor for it to have any lasting effects.

We will measure:

- Your behaviour on several different tasks

WHAT DOES PARTICIPATION IN THIS STUDY INVOLVE?



INTAKE Session. Before you can take part in the research, you would first make an appointment for an intake session. You will complete a number of questionnaires and one of the researchers will go through a list of questions with you. Your answers to the questions are important for the study, but also for your own safety. Pregnant or breastfeeding women and people with an increased risk of glaucoma cannot participate in the study for safety reasons. At the intake session, your blood pressure, heart rate, and an electrocardiogram (ECG) will be measured. For the ECG measurement, you will have to undress from the waist up and the experimenter or medical personnel will attach electrodes to your chest and limbs. These measurements are necessary to determine whether you can take sulpiride without risk. When deciding whether you are eligible to participate, the researchers will err on the side of caution: if we decide on the basis of these measurements that you are not allowed to participate, it does not mean that you are not healthy. The first visit will conclude with some baseline cognition measurements and some training on the cognitive tasks. We will also answer any questions you have.

If, on the basis of this first visit, you can and want to participate, two appointments will be made with you to come to the research center to be tested with you to come to the research center to be tested.

Test Sessions

These two test sessions do not differ from each other, except that you will receive sulpiride on one of the sessions and placebo on the other. You will also be asked to complete a number of online questionnaires before the last test day. The second test day will take place at least one week and no later than 2 months after the first session. Prior to each test day, it is important thatyou have not consumed alcohol for 24 hours, have not used any other narcotics for at least 72 hours, do not smoke on the morning of the test day, and have had breakfast in the morning.

Smoking and drinking stimulant drinks (e.g. with caffeine) are not allowed on the test days.

On the medication testing days, you will come to the Donders Center for Cognitive Neuroimaging in Nijmegen in the morning. First you will be asked to fill in some questionnaires. Women will undergo a pregnancy test to rule out pregnancy. Then, after measuring blood pressure, heart rate, and body temperature, which will be repeated two more times each test day, you will be given a capsule (either sulpiride or placebo).

The capsules you will receive will contain one of the following (you will receive both in the study, one on each testing day):

- 400 mg sulpiride
- placebo

The order of receiving sulpiride or placebo will be double-blind. That is, it differs per participant whether they receive sulpiride or placebo on the first or second day. The order will be unknown to both you and the experimenter who is testing you.

This standard procedure is necessary to prevent our own expectations from affecting the results. You will first do a memory task, which will take approximately 1 hour After completing the task, we will serve you a light lunch. After lunch you will be asked to complete a number of other computer-based tasks, which will take approximately 1 hours. At the end of the session, we will test your driving skills. We ask that you do not drive or ride a bike to your appointment because sulpiride can affect your driving ability (see Burdens and Risks below). If needed, a taxi will be arranged to take you home.

FINANCIAL COMPENSATION

The financial compensation for participation in this study has been determined as follows:

Time investment: €10/hour *(5.5 hours * 2 sessions + 3 hours intake, + 1 hour at	home)	€150,-
Extra payment for intake of medication: €10 * 2 sessions		€20,-
Bonus payment for task performance: up to €10 * 2 sessions	up to	€20,-
Total	up to	€190,-

BURDENS AND RISKS

SULPIRIDE: We do not expect any serious side effects from a single administration of sulpiride at this dose. Sulpiride can in exceptional cases cause drowsiness, mild nausea and vomiting.
For this reason, you will remain under medical supervision during the period that sulpiride is active. Because sulpiride could affect your ability to drive (including biking), we ask that you do not participate in traffic for at least 24 hours after the end of the study. Sulpiride may also affect alertness. Although we think this is unlikely, we therefore recommend that you do not engage inactivities that require alertness for up to 24 hours after ingestion. After 24 hours, the level of sulpiride in your blood will have dropped below 10 percent and will no longer have any noticeable effects. In an earlier study using the same dose of sulpiride (https://www.trialregister.nl/trial/5959), none of the participants reported a feeling of reduced alertness 24 hours after taking sulpiride. We recommend that you read the package leaflets for sulpiride (see appendix) before deciding to participate in this study.

OTHER PROCEDURES: All procedures followed in this study are harmless. However, some procedures can be experienced as unpleasant or uncomfortable. In addition, participation takes a lot of time, because you have to spend time on three different days in the Donders Center for Cognitive Neuroimaging. The decision about whether you would like to participate, given these potential burdens, is one that you must make yourself.

INCIDENTAL MEDICAL FINDINGS

It is very important that you realize the following: there is a small but real chance that new information will be discovered regarding your health status during your participation in this study(for example via the ECG recordings). Such information will have nothing to do with the research question of the study, but may have medical consequences for you. These are called 'incidental findings'. If there is such an incidental finding, the research team, including a medical doctor, will decide whether it is medically relevant. If the finding is medically relevant, you will beinformed. If you do not wish to be informed about this, you cannot participate in this study.

However, we want to emphasize that the researchers at the DCCN do not examine the data acquired from a medical perspective. Participation in any of the experiments cannot be considered as a medical nor screening test. The study should not be seen as a medical test.

Pros and cons of incidental findings: In order to make an informed decision, it is important that you weigh the pros and cons of incidental findings. These are described below. Knowledgeof an incidental finding has the advantage that timely medical measures can be taken. This may prevent or reduce the risk of getting a medical condition, or reduce its impact. However, the knowledge of an incidental finding can also have drawbacks. It can be psychologically stressful, to know about a health problem that may develop in the future. This disadvantage applies in particular if the available medical treatments for the condition are only of limited help or drastic. Knowledge of an incidental finding can also have financial and social consequences, for example when taking out life or disability insurance. Knowledge of an incidental finding also means that your relatives can learn that they may also have a hereditary predisposition to the relevant condition. This may have the same advantages and disadvantages for your family member.

INSURANCE

This research is not dangerous to health. However, the Donders Institute is legally obliged to take out insurance for every examination. This insurance is part of the insurance for participants in research at Radboud University Nijmegen. This insurance has been taken out with Centramed BV (see below for full information).

PRIVACY AND CONFIDENTIALITY OF DATA

All collected data will be treated confidentially. For scientific publications, data is processed without your name and personal information. The medical data relevant to the study can only beviewed by employees involved in the study. All this is described in the privacy regulations of theDonders Institute. Interested parties can view the regulations at the secretariat of the Donders Institute or request a copy by email.

RIGHT OF ACCESS

Some other people can view your research data on request. These people check whether the research is carried out properly and reliably. These people are, for example: the research team, an audit team, the review committee or the Public Health Inspectorate.

SHARING YOUR RESEARCH DATA

Sometimes we want to share your coded, anonymised research data with other researchers for strictly scientific purposes. If you prefer that your anonymized data are not shared, we of course understand; however you will not be eligible to participate in the study.

STOP THE INVESTIGATION

Your participation in this study is completely voluntary and you can withdraw from this study at any time. The researchers also have the right to stop this study or your participation in the studyat any time. In all cases of early termination of participation, you will be paid for the componentsof the study in which you have participated.

IF YOU WANT TO PARTICIPATE IN THE RESEARCH

You will be contacted by a member of the research team one week after this information brochure has been provided to ask whether you have made a decision about your participation. To participate in the study, you must also meet a number of medical criteria. For this we have drawn up a short medical questionnaire (see below). We ask you to complete this questionnaire before we make an intake appointment with you. The researchers will discuss these questions with you by telephone. If you must answer 'yes' to any of the questions, you will not be able to participate in the study. You do not need to indicate to which question the 'yes' applies. If you donot answer 'yes' to any of the questions, an intake appointment will be made. Only after this appointment can we decide whether you can take part in the study.

Before participating in this study, it is necessary to sign a declaration of consent ("informed consent"; see below). The consent form will be reviewed and signed at the start of the intake session. In this form, you declare, among other things, that you are well-informed about the study, that your questions have been satisfactorily answered, and that you have been informed that you may withdraw your consent to participate in the study at any time. You also hereby givepermission to be approached for follow-up research. Participation in this possible follow-up study is of course also completely voluntary.

FURTHER INFORMATION

If you have any questions about this research, please contact one of the researchers:

Floortje Spronkers, Donders Center for Cognition, Thomas van Aquinostraat 4, NijmegenTel: 31-24-3612605 (speaks Dutch and English)
E-mail: f.spronkers@donders.ru.nl

If you wish, you can also contact an independent researcher, who is not involved in conducting this study, for information and advice:
Dr. Rick Helmich, Donders Center for Cognitive Neuroimaging, Kappitelweg 29, NijmegenTel: 31-024-3610983
Email: r.helmich@donders.ru.nl

With best regards, The research team

Floortje Spronkers
Dr. Hanneke den Ouden
Prof. Dr. Roshan Cools

INFORMATION BROCHURE

The Donders Centre for Cognitive Neuroimaging at the Trigon building, Kapittelweg 29, is open for scientific research in volunteers. With this extra information brochure, we would liketo inform you about the precautions measures in place.

We always follow the COVID-19 guidelines and advise of the National Institute for Public Health & Environment / RIVM : this forms the basis for our precaution measures. We takethese measures to ensure safety for you as participant as well as for our researchers.

We would like to emphasize to stay at home in case:

- **YOU HAVE ONE OR MORE OF THE FOLLOWING SYMPTOMS IN THE PAST 24 HOURS : COUGHING, SYMPTOMS OF A COMMON COLD, FEVER OR ELEVATED TEMPERATURE, SHORTNESS OF BREATH,LOSS OF TASTE AND SMELL.**
- **ANYONE IN YOUR HOUSEHOLD HAS MILD SYMPTOMS ACCOMPANIED BY FEVEROR SHORTNESS OF BREATH**
- **YOU HAVE A NOVEL CORONAVIRUS INFECTION (LABORATORY-CONFIRMED IN THE PAST 7 DAYS)**
- **YOU ARE IN QUARANTAINE BECAUSE:**
  - **YOU HAD CLOSE CONTACT WITH OR SOMEONE WITH A CONFIRMED COVID-19 INFECTION**
  - **SOMEONE IN YOUR HOUSEHOLD HAD A CONFIRMED COVID-19 INFECTION**
  - **YOU HAVE BEEN IN A COVID-19 HIGH-RISK AREA***
  - **YOU RECEIVED A NOTIFICATION FROM THE CORONAMELDER-APP**

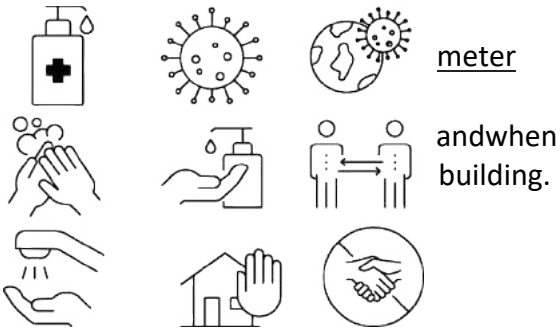
*area's can be found on www.netherlandsworldwide.nl/travel

In case of doubt or questions, please contact the researcher to avoid coming in vain.

When visiting the center at the Trigon building, Kapittelweg 29, you are welcomed by one ofthe centers employees. The employee will verbally go through together with you the indicated checklist.

We ask you politely to:

- arrive punctually on the agreed time and keep 1,5 distance inside and outside the building.
- Wear a mouth mask when entering the building moving from one location to another inside the
- disinfect your hands on arrival
- not shake hands.



meter

andwhen building.

For certain research it is not possible to meet the 1,5 meter distance: e.g. preparation for participation in MRI. EEG/ MEG and tACS/ TMS research. In that case the experimenter will follow the protocol in place and take whenever applicable additional protective measures. Weask you to follow the instructions of the dedicated personnel. Please feel free to ask questions with respect to the precaution measures preferably in advance or during participation. The experimenter is happy to answer any questions.

COVID-19 information brochure version 5.0; January 20th 2021

Insurance text

For participants of all research at the Donders Centre for Cognitive Neuroimaging, a standard medical liability insurance is established.

For some studies, an additional law-imposed subject insurance is established. This insurance covers losses caused by death or injury resulting from participation in this scientific research, which reveals itself during the participation of the subject in the scientific research or within four years thereafter. The personal injury is deemed to have revealed itself at the time it is reported to the insurer.

In the event of a claim, you may contact the insurer directly.

The insurer is:

Onderlinge Waarborgmaatschappij Centramed B.A.

P.O. Box 7374
2701 AJ Zoetermeer, The NetherlandsTel.:
+31 70 3017070
Email: Schade@centramed.nl

The insurance provides a maximum coverage of € 650,000 per subject and € 5,000,000 for the entire research, and € 7,500,000 per annum for all examinations of the same client.

The above amounts are included in the "Besluit verplichte verzekering bij medisch-

wetenschappelijk onderzoek met mensen". Information on this "besluit" can be found at the website of the Central Committee Clinical Research Involving Human Subjects: www.ccmo.nl.

The insurance covers losses resulting from experiments. The insurance does **not** cover:

- claims for injury that is inevitable or practically inevitable, given the nature of the experiment
- injury to the health which also would have occurred if you had not participated in the experiment
- injury caused by the subject's non- or partial adherence to directions or instructions
- injury to the descendent(s), as a result of an adverse effect of the experiment on the subject or
- on the subject's descendent(s)
- injury caused by an existing treatment method in an experiment into existing treatment methods
- injury resulting from the occurrence of a risk of which the subject was warned in the written information, unless the risk occurs in a more serious degree than was expected or said risk was highly unlikely to occur

Medical Questionnaire

Below are questions about your medical history, which are important for your eligibility to participate in the study. All answers can be answered with a yes or no. We would like to ask youto complete this form at home. If your answer to any of the questions is “yes”, unfortunately you (probably) will not be able to participate in the study.

If in doubt, you can ask your GP or contact the researcher at the Donders Centre. In that case,extra space has been left open for you to comment on your answer.

Have you suffered from an existing chronic condition in the past 12 months and are you under medical supervision or treatment for this?

yes/ no

Are you currently or have you in the past been diagnosed with a psychiatric disorder*and are you under medical supervision or treatment? (*for example, depression, anxiety disorder, schizophrenia, anorexia)

yes/ no

Have you currently or in the past been diagnosed with a neurological disorder* and areyou under treatment or medical supervision for this? (*with the exception of headaches)

yes/ no

Have you currently been diagnosed with either glaucoma or elevated intraocular pressure* and are you under medical supervision or treatment for this? (*with the exception ofheadaches)

yes/ no

Have you currently been diagnosed with either an endocrine or hormonal disorder* andare you under medical supervision or treatment for this? (*for example Cushing’s or Addison’s Disease, or thyroid disease)

yes/ no

Have you been diagnosed with a metabolic disorder* now or in the past and are youunder medical supervision or treatment for this? (*for example diabetes)

yes/ no

Have you currently been diagnosed with obstructive lung disease* and are you undermedical supervision or treatment for this? (*for example asthma or chronic bronchitis)

yes/ no

Have you ever been diagnosed with a heart condition, such as an irregular heartbeatand are you under medical supervision and treatment?

yes/ no

Have you ever been diagnosed with anemia and are you currently under medicalsupervision or treatment?

yes/ no

Have you ever been diagnosed with hyperthyroidism (increased thyroid production) andare you under medical supervision or treatment for this?

yes/ no

Have you ever been diagnosed with kidney problems and are you under medicalsupervision or treatment for this?

yes/ no

Have you ever been diagnosed with high blood pressure and are you under medicalsupervision?

yes/ no

Are you currently suffering from an acute infection (fever can be a symptom)?

yes/ no

Do you regularly suffer from vertigo? yes/ no

Do you have an allergy, such as lactose intolerance or any allergies (such as eczema, hayfever (hooikorts))?

yes/ no

Do you have poor vision that cannot be fixed by glasses or contact lenses?

yes/ no

A) Do you take medicine*? yes / no
(*with the exception of contraceptive medicine, homeopathy, herbal extracts or supplements,such as vitamins)

B) Bent U overgevoelig voor bepaalde methylfenidaat? yes / no
Zo ja welke:……..

Would you have a problem with not smoking, not drinking alcohol and not using drugsfor 24 hours before each test day??

Do you have family members who suffer from heart problems, mainly an irregularheartbeat, for which they are treated?
Father/mother, brothers/sisters: yes/ no
More than one grandparent, uncle or aunt (not by marriage): yes/ no

Do you have family members who suffer from schizophrenia or bipolar disorder?Father/mother, brothers/sisters:
yes/ no

Do you practice top-level sport? yes/ no

Do you suffer from claustrophobia? yes / no

Do you sometimes faint in certain situations (e.g., when having blood taken or standingfor a long time?)
yes / no

Do you have any metal objects in your body? Exception: dental fillings or crowns?
yes / no

Do you have problems with lying still for ~1.5 hours?
yes / no

Do you have problems with swallowing large pills?
yes / no

INFORMED CONSENT FORM
For participation in: "DOPAMINE AND COGNITIVE FUNCTION"

To be filled in by the PARTICIPANT before the start of the study:

I confirm that:

- I am satisfactorily informed about the study concerned, both orally and in writing, by means of the study-specific information brochure (CMO 2020-7199, version 4).
- I have had the opportunity to put forward questions regarding the study and that these questions have been answered satisfactorily
- I have carefully considered my participation in the experiment.
- I participate of my own free will.

I agree that:

- My data will be collected and used for the purpose mentioned in the information brochure.
- I will be informed by my home physician or the academic GP of General Practitioner Center Heijendaal about any new information which is of medical relevance to me.
- I can be contacted about participating in a future study
- Beyond the scope of this study: my anonymized experimental data will be shared with other researchers or research groups

I understand that:

- I have the right to withdraw from the experiment at any time without having to give a reason.
- I have the right to request disposal of my experimental data up to 1 month after participation
- My data will be protected according to applicable European privacy law.
- My consent will be sought every time I participate in a new experiment.
- For compliance check of the research few persons may have access to my (personal) data. These persons are mentioned in the information brochure. I consent for this.

I give my consent to take part in this experiment:

Name:…… Date of Birth ……(dd/mm/yy)

Signature:…… Date and Place:……..

To be filled by the RESEARCHER prior to the start of the experiment:

The undersigned declares that the person named above has been informed both in writing and in person about the experiment. He /she guarantees subjects' privacy protection.

Name:…… Project Code:……

SONA Study Title:……

Signature:…… Date (dd/mm/yyyy):……

Supplementary material 2 – Additional results

Figure S01 – Session effects pharmacology sample

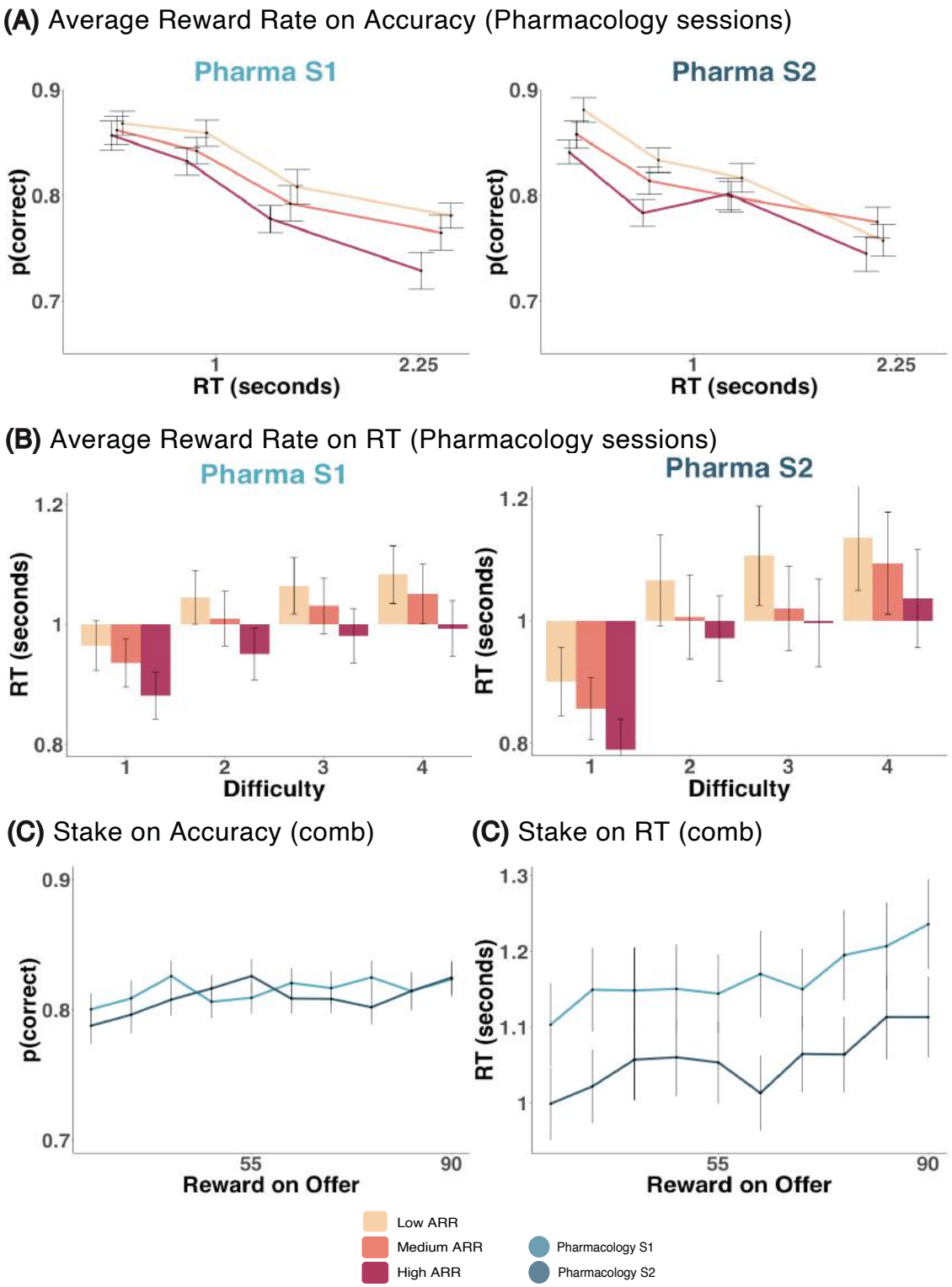


Figure S01: Main effects per session. **(A)** Effect of RT on accuracy for high, medium, and low average reward rate. **(B)** Interaction of average reward rate and difficulty on RT. **(C)** Stake and accuracy. **(D)** Stake and RT