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ORIGINAL INVESTIGATION

Effects of average reward rate on vigor as a function of individual variation in striatal dopamine

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Abstract

Rationale We constantly need to decide not only which actions to perform, but also how vigorously to perform them. In agreement with an earlier theoretical model, it has been shown that a significant portion of the variance in our action vigor can be explained by the average rate of rewards received for that action. Moreover, this invigorating effect of average reward rate was shown to vary with within-subject changes in dopamine, both in human individuals and experimental rodents.

Objectives Here, we assessed whether individual differences in the effect of average reward rate on vigor are related to individual variation in a stable measure of striatal dopamine function in healthy, unmedicated participants.

Methods Forty-four participants performed a discrimination task to test the effect of average reward rate on response times to index vigor and completed an [^{18}F]-DOPA PET scan to index striatal dopamine synthesis capacity.

Results We did not find an interaction between dopamine synthesis capacity and average reward rate across the entire group. However, a post hoc analysis revealed that participants with higher striatal dopamine synthesis capacity, particularly in the nucleus accumbens, exhibited a stronger invigorating effect of average reward rate among the 30 slowest participants.

Conclusions Our findings provide converging evidence for a role of striatal dopamine in average reward rate signaling, thereby extending the current literature on the mechanistic link between average reward rate, vigor, and dopamine.

Keywords Dopamine · Average reward rate · Opportunity cost · Vigor · PET · Individual differences

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Introduction

Behaving animals, including humans, constantly have to make choices about which action to perform in order to maximize reward. Additionally, after choosing an action, one has to decide how much effort to put into performing that chosen action, or how fast to perform it. These types of decisions have been linked to the ascending neuromodulatory systems, including the cholinergic nucleus basalis of Meynert (Khalighinejad et al. 2020) and the midbrain dopamine system. Phasic dopamine signals in the midbrain and the striatum represent reward prediction errors, which can be used for learning the expected value of the outcome of particular actions and therefore learning which actions to choose to maximize reward (Schultz et al. 1997; D'Ardenne et al. 2008). Another large body of literature has shown that increases in dopamine are related to increases in the vigor of actions, or behavioral activation (decreased action latency) (Ikemoto & Panksepp 1999; Salamone & Correa 2002; Robbins & Everitt 2007). For example, intra-accumbens

microinjection of the psychostimulant *d*-amphetamine in rats enhances responding for reward-related stimuli in a conditioned reinforcement paradigm (Taylor & Robbins 1984), which was shown to specifically depend on dopaminergic activation using combined 6-OHDA dopamine lesioning and administration of the dopamine agonist apomorphine (Taylor & Robbins 1986). Similarly, a dopamine lesion using the neurotoxic 6-OHDA in the core of the nucleus accumbens reduced the rate of responding in a fixed ratio paradigm in which rats had to press a lever in return for a food reward (Sokolowski & Salamone 1998).

An influential theory by Niv and colleagues (Niv et al. 2007) integrates these lines of literature, linking value signals and vigor in a formal model that incorporates a signal for an agent's average reward rate, which is reported by dopamine, putatively in the nucleus accumbens. How much reward one expects to gain for an action within a certain period of time can be predicted by the average rate of rewards received in a preceding period. If this average reward rate is high, it is more costly to act slowly, because this would delay the delivery of a relatively high reward. Therefore, dopamine, which is thought to signal the average reward rate, would offset the intrinsic cost of acting fast, and thereby promote vigor (fast responding). This hypothesis thus addresses a key link between dopamine signaling, reward and action vigor (Cools et al. 2011). This notion of dopamine offsetting intrinsic effort costs is related to a recent framework of "rational inattention" stating that agents can increase their performance on a task by paying the cost of extra cognitive or attentional effort, which is only worthwhile when the average reward rate, reported by tonic dopamine, is high (Mikhael et al. 2021).

Experimental work has supported the theory by Niv et al. (2007) by demonstrating that people respond faster when the average reward rate is higher on tasks requiring attentional discrimination (Guitart-Masip et al. 2011; Beierholm et al. 2013), cognitive control, perceptual decision-making, and task-switching (Otto & Daw 2019). Moreover, there is empirical evidence that the average reward rate signal is carried by dopamine (Niv et al. 2007): The invigorating effect of average reward rate was stronger for individuals after administration of 150 mg of oral levodopa, a precursor of dopamine, than placebo (Beierholm et al. 2013) and single-unit recordings of midbrain dopamine neurons in macaque monkeys showed that tonic firing continuously tracked moment-by-moment fluctuations in reward values in a Pavlovian procedure (Wang et al. 2021). Furthermore, recent microdialysis studies have demonstrated that fluctuations in reward rate, indexed by the number of recently rewarded trials, were associated with rapid fluctuations in dopamine levels in the nucleus accumbens, as well as enhanced motivational vigor in rats performing a trial-and-error task (Hamid et al. 2016; Mohebi et al. 2019).

The possible range of dopamine levels is related to the capacity of the system to synthesize dopamine. Although the link between dopamine synthesis capacity, as indexed by [^{18}F]-DOPA uptake, and dopamine release is unclear (Berry et al. 2017), there is converging evidence for links with dopamine D2/3 receptor binding (Ito et al. 2011; Berry et al. 2017), response to D2/3 receptor antagonists, used as antipsychotic treatment in schizophrenia (Howes et al. 2009; Veronese et al. 2021), as well as functional and clinical progression of Parkinson's disease (Nagano-Saito et al. 2004; Koerts et al. 2007; Pavese et al. 2011). The functional relevance of [^{18}F]-DOPA uptake for dopamine signaling is further substantiated by accumulating evidence for between-subject correlations with dopamine-related cognitive task performance (Deserno et al. 2015; Hofmans et al. 2020; Westbrook et al. 2020). While dopamine synthesis capacity differs across individuals, it is relatively stable over time within one individual (Egerton et al. 2010). In this study, we therefore shift attention away from the role of within-subject fluctuations in dopamine towards the role of between-subject differences in stable dopamine synthesis capacity. Choice biases are now well established to vary greatly across different individuals, and such individual variation is thought to account for considerable variability in psychiatric symptomatology and treatment efficacy (Collins & Frank 2014; Huys et al. 2021). For example, we have recently shown that [^{18}F]-DOPA uptake, a stable trait index of striatal dopamine synthesis capacity, predicts individual differences in choices about which action to perform, as well as the effect of methylphenidate on such choices (Hofmans et al. 2020; Westbrook et al. 2020). Here, we build on this work and ask whether the effect of average reward rate also differs depending on individual variation in dopamine synthesis capacity, specifically in the nucleus accumbens, in healthy, unmedicated participants. To this end, we invited participants, who had previously completed an [^{18}F]-DOPA positron emission tomography (PET) scan, to return to the institute. These participants then performed exactly the same discrimination task as employed previously to quantify the effect of average reward rate on vigor (Guitart-Masip et al. 2011; Beierholm et al. 2013). Based on the theory by Niv et al. (2007) and experimental findings described above (Hamid et al. 2016; Mohebi et al. 2019), we predicted that the effect would be most pronounced in the nucleus accumbens, as such also extending the finding by Beierholm et al. (2013) by demonstrating regional selectivity. Thus, our primary analyses focused on the nucleus accumbens, although we also explored dopamine function in the more dorsal putamen and caudate nucleus.

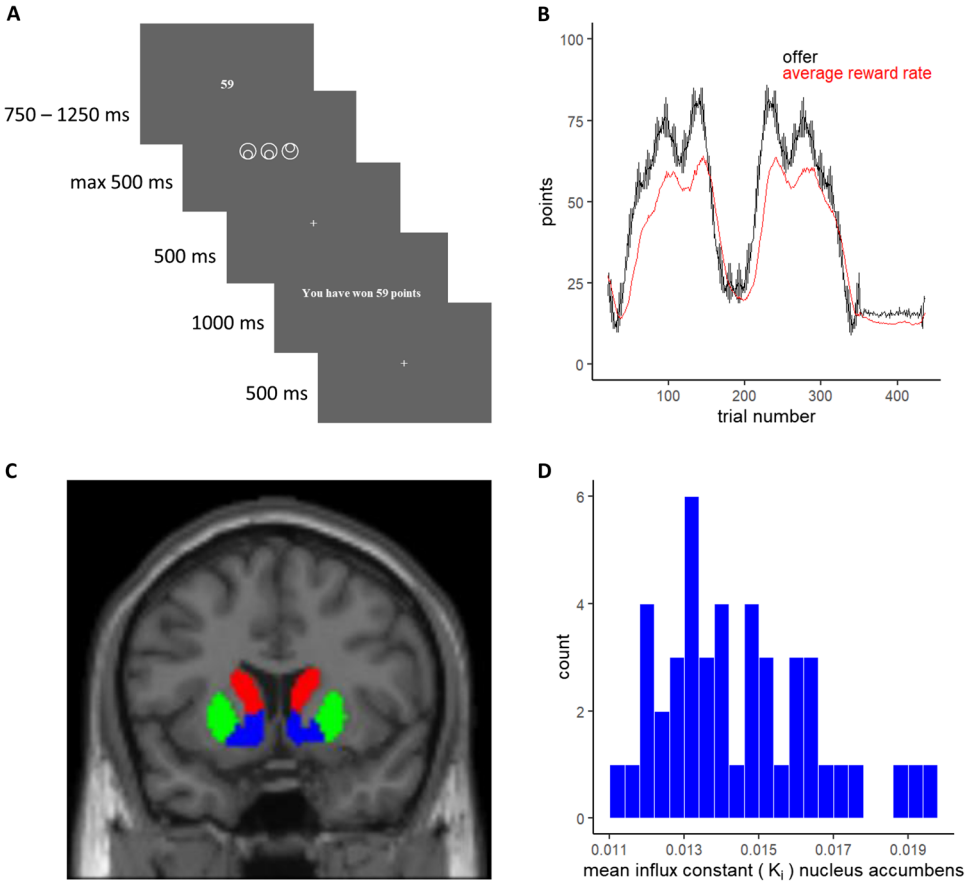

Fig. 1 Schematic of the study. **A** Depiction of the oddball task. **B** Offered reward and average reward rate (mean value across participants) for learning rate $\alpha = 0.1133$ (the average learning rate across subjects found by Beierholm et al. (2013) when they reanalyzed the dataset from Guitart-Masip et al. (2011)). **C** Coronal view of our three regions of interest including the nucleus accumbens (blue), putamen (green), and caudate nucleus (red). **D** Histogram of mean K_i value in the nucleus accumbens

Methods

Participants

Forty-five (out of a total of 94) right-handed and native Dutch-speaking volunteers who had participated in a previous [^{18}F]-DOPA PET study (protocol NL57538.091.16; trial register NTR6140, www.trialregister.nl/trial/5959) accepted the invitation to participate in the current study. All participants gave written informed consent according to the declaration of Helsinki and the experiment was approved by the local ethics committee (CMO Arnhem-Nijmegen, The Netherlands; Imaging Human Cognition, CMO 2014/288, version 2.2). One dataset was excluded because the participant did not respond on any of the trials. This resulted in 44 participants (21 women; age: 19–45 years, mean = 24.3, SD = 5.8). The time between the PET scan and this behavioral study ranged between 0.3 and 1.8 years (mean = 1.0, SD = 0.4).

Behavioral oddball task

The task (Fig. 1A) was performed on a computer running on Windows 7 with a screen resolution of 1920 × 1080p and a grey background color (R: 200 G: 200 B: 200). The task was programmed in MATLAB version 2017b, using Psychophysics Toolbox Version 3.0.12. In each trial, participants were offered a reward ranging between 5 and 95 points, according to a function specified in Guitart-Masip et al. (2011) and Beierholm et al. (2013), which was fixed across participants (Fig. 1B). This offer remained on screen for a variable period, ranging between 750 and 1250 ms; after which, three stimuli appeared on screen. Participants had to pick the odd one out by pressing a button on the number pad of a regular keyboard (by pressing 1, 2, or 3, corresponding to the location of the odd one out). If they gave the correct response within 500 ms, they received the offered reward. This time limit was lowered to 400 ms on 20% of the trials to promote task engagement. After a blank screen was presented for 500 ms, a feedback screen was presented for 1000 ms, informing the participants about their performance and received reward. Another blank screen was presented for 500 ms, after which the next trial started. Participants completed as many trials as possible within a time window of 27 min and received a monetary bonus proportional to their summed reward. Thus, the more trials they completed, the more money they could win.

PET acquisition

PET scans were acquired at the Department of Nuclear Medicine of the Radboud University Medical Center, using a Siemens PET/CT scanner (Siemens Biograph mCT) and the radiotracer [^{18}F]-DOPA. Participants received 150 mg of carbidopa and 400 mg of entacapone 50 min before scanning, to minimize peripheral metabolism of [^{18}F]-DOPA and thereby increase central [^{18}F]-DOPA availability. The procedure started with a low-dose CT scan (approximately 0.75 mCi) followed by a bolus injection of approximately 185 MBq [^{18}F]-DOPA into an antecubital vein and an 89-min dynamic PET scan (mean tracer dose = 184.2 MBq, SD = 10.2 MBq; approximately 5 mCi; molar activity approximately 50–100 GBq/μmol). The data were divided into 24 frames (4 × 1, 3 × 2, 3 × 3, 14 × 5 min) and images were reconstructed using the Siemens TrueX algorithm with weighted attenuation and scatter correction and time-of-flight recovery. The reconstruction used 3 iterations with 21 subsets and Gaussian post-reconstruction smoothing was applied using a 3-mm full width at half maximum (FWHM) kernel.

Structural MRI

A high-resolution T1-weighted anatomical MRI scan was acquired using an MP-RAGE sequence (repetition time = 2300 ms, echo time = 3.03 ms, 192 sagittal slices, field of view = 256 mm, voxel size 1 mm isometric) on a Siemens 3 T Magnetom Skyra MR scanner with a 64-channel coil. These were used for coregistration and spatial normalization of the PET scans.

PET analysis

PET data were preprocessed and analyzed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). All frames were realigned for motion correction and coregistered to the anatomical MRI scan, using the mean PET image of the first 11 frames. Dopamine synthesis capacity was computed as the [^{18}F]-DOPA influx constant (K_i) per minute per voxel relative to the grey matter of the cerebellum, using the Gjedde–Patlak graphical analysis (Patlak et al. 1983). The individual cerebellum grey matter masks were obtained by segmenting the individuals' anatomical MRI scan, using Freesurfer (https://surfer.nmr.mgh.harvard.edu/). The K_i values were calculated based on the PET frames from the 24th to 89th minutes, during which striatal [^{18}F]-DOPA appears to be irreversibly trapped in presynaptic vesicles in the terminals of dopaminergic neurons, and [^{18}F]-DOPA influx, or the ratio of striatal and cerebellar radioactivity over time, is linear (Patlak et al. 1983; Sossi et al. 2001, 2002) (Fig. 2). We then extracted average K_i values from three regions of interest (ROIs) — nucleus accumbens, putamen, and caudate nucleus — defined using masks based on an independent functional connectivity analysis of the striatum (Piray et al. 2017) (Fig. 1C-D). A prior study has shown good test–retest reliability of this procedure to assess dopamine function, with intraclass correlation coefficients ranging from 0.738 to 0.944, using a 2-year scan interval (Egerton et al. 2010).

We supplemented the ROI-based analyses with exploratory voxel-wise regression analyses of dopamine synthesis capacity on the effect of average reward rate on response times (see below). To this end, the individual K_i maps were spatially normalized to MNI space and smoothed using an 8-mm FWHM kernel.

Data analysis

Participants with fewer than 200 trials that were correct and within the time limit were excluded from the analyses. Missed trials (without any response) were excluded from the analyses, as were the first 20 trials to allow for a practice period. Following the analysis of Beierholm et al. (2013), response times were log-transformed. We subsequently removed all trials with a log-transformed response time that was more than three standard deviations from the individual mean (Beierholm et al. 2013). We then recalculated the individual mean log-transformed response times and again removed all trials which deviated more than three standard deviations from the individual mean response time, after which we z-scored each participant's log-transformed response times (Beierholm et al. 2013).

We performed a linear regression on the log-normalized response times using Bayesian mixed effects modeling, which takes into account each single trial, using the brm function from the brms package (Bürkner 2017) in R version 3.4.2 (R Core Team 2018). The following regressors were included in the model (model 1):

An intercept.

$\overline{R_t}$: continuous variable indicating the average reward rate (Fig. 1B), as given by a Rescorla–Wagner updating function: $\overline{R_t} = \overline{R_{t-1}} + \alpha(R_{t-1} - \overline{R_{t-1}})$,
where R_{t-1} is the reward received on the previous trial and α is the learning rate. This learning rate was set to 0.1133, following the analysis in Beierholm et al. (2013) on the original dataset in Guitart-Masip et al. (2011)
Offer: continuous variable indicating the available reward for the participant to win on the current trial.
Repetition of stimulus: binary variable indicating whether the position of the odd stimulus on the current trial was the same as in the previous trial.
Trial number: continuous variable.

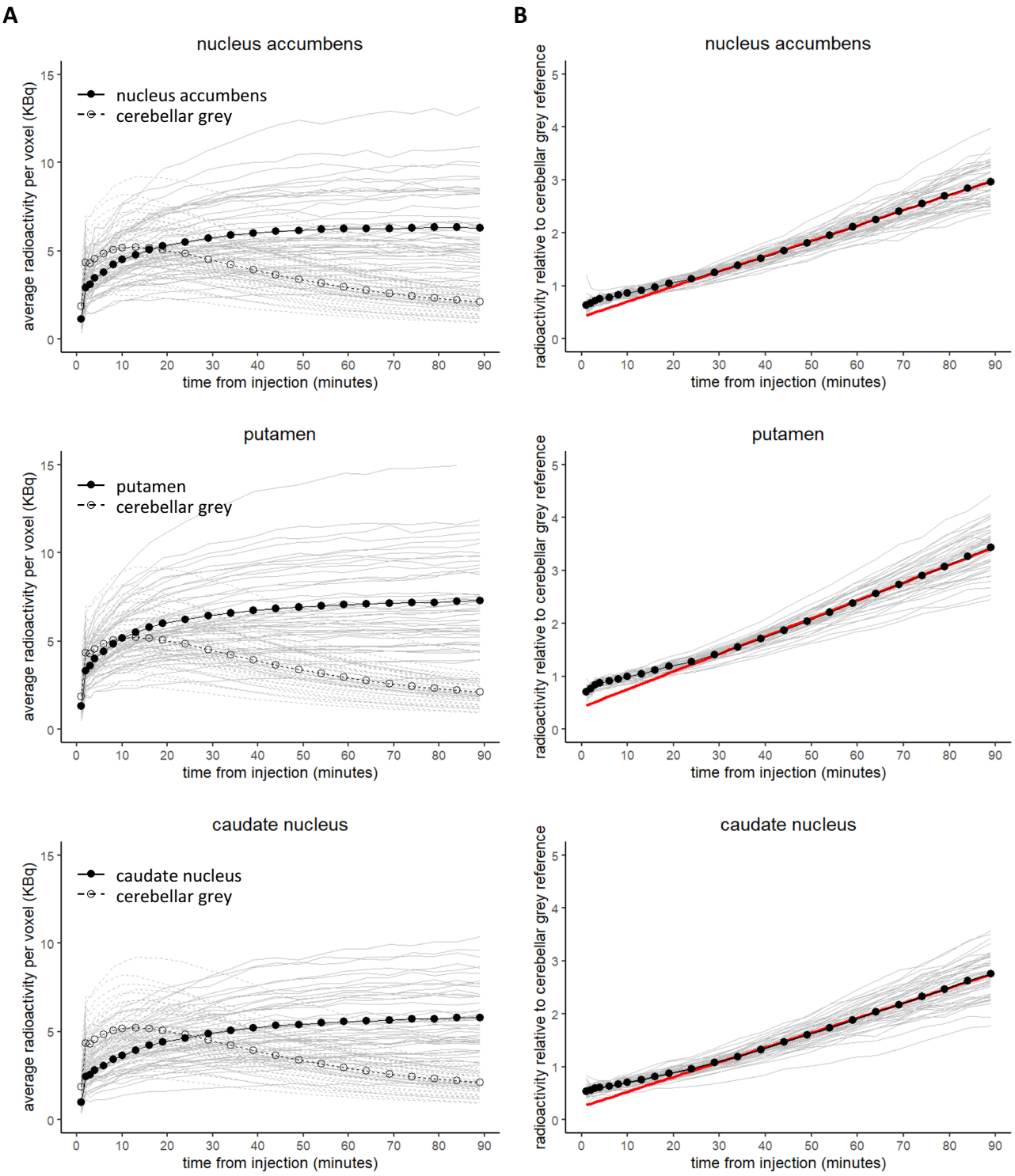

Fig. 2 Time-activity curves. **A** Radioactivity in cerebellar grey and each striatal region of interest at each timepoint. **B** Radioactivity in each striatal region of interest at each timepoint, divided by radioactivity in cerebellar grey. Calculation of K_i values was based on PET frames from the 24th to 89th minute, during which [^{18}F]-DOPA influx, or the ratio of striatal and cerebellar radioactivity over time, is approximately linear. Red line represents linear fit from the 24th to 89th minute; grey lines represent individual participants

Late previous: binary variable indicating whether the participant responded too late on the previous trial.
Offer duration: continuous variable indicating the duration of the presentation of the offered amount prior to presentation of the oddball stimulus.
K_i: a continuous variable indicating dopamine synthesis capacity.
$K_i \overline{R_t}$: an interaction term between dopamine synthesis capacity and average reward rate.

All regressors were included as fixed effects. Additionally, a random intercept and random slopes for all regressors were included per participant, except for dopamine synthesis capacity and its interaction with average reward rate, for which there was only one value per participant for each target brain region. All continuous regressors were *z*-scored to improve model interpretability. Given the already log-normalized response times, we used a Gaussian family function. We used default brms-priors. The model was fit using four chains with 10,000 iterations each (5000 warm-up) and were inspected to ensure convergence. Coefficients were considered statistically significant if the 95% posterior credible intervals did not overlap with zero. We first performed the regression analysis for our main ROI, the nucleus accumbens, followed by exploratory regression analyses for both the putamen and the caudate nucleus.

To assess the physiological plausibility of the effect, we conducted an additional exploratory whole-brain analysis. To this end, we extracted the individual regression coefficients (the sum of the fixed (group level) coefficient and the random (individual level) coefficient) of average reward rate on response times from a model excluding dopamine synthesis capacity as a regressor (model 0). We then performed a voxel-wise regression analysis of dopamine synthesis capacity (K_i) on these regression coefficients.

To assess whether a potential interaction with dopamine synthesis capacity was specific to average reward rate, we ran a control analysis in which dopamine synthesis capacity interacted with all other regressors (model 2; Fig. 5B).

Dopamine synthesis capacity and therefore the interaction effect between dopamine synthesis capacity and average reward rate on vigor could potentially be affected by variables of no-interest, such as age (DeJesus et al. 2001; Ota et al. 2006; Kumakura et al. 2010; Berry et al. 2016), sex (Laakso et al. 2002), the time delay between PET acquisition and behavioral testing, and tracer dose. To control for any potential effects of these variables of no-interests, we conducted a control analysis including the additional predictors age (in years), sex, the time delay between PET acquisition and behavioral testing (in days), and tracer dose (MBq per KG of body weight), including their interaction with average reward rate (model 3). All of these additional predictors were added as fixed effects only, given that there is only one value per participant (Table 1).

Results

Independent of whether they responded within the time window, participants chose the correct response on 91.8% of trials, similar to earlier results (Guitart-Masip et al. 2011; Beierholm et al. 2013). The mean individually averaged response time across all trials was 394.6 ms, which is substantially faster than in the earlier studies (Guitart-Masip: mean: 415.0 ms; Beierholm: 403.9 ms). Participants responded correctly and within the time window (and thus received a reward) on 81.2% of trials. The mean and standard deviation of the K_i values, representing dopamine synthesis capacity are comparable to previous reports (Sossi et al. 2002; Egerton et al. 2010; van Holst et al. 2018). Table 2 displays the means and standard deviations of the behavioral data and measures of dopamine synthesis capacity.

Analysis of entire participant group reveals no relationship between dopamine synthesis capacity in the nucleus accumbens and the effect of average reward rate on vigor

Contrary to our hypothesis, we did not find a main effect of average reward rate on response times (CI = [− 0.024, 0.065]), nor did we find an interaction between dopamine synthesis capacity in the nucleus accumbens and average reward rate (CI = [− 0.047, 0.011]). In keeping with the earlier studies, we also found no effect of the immediate monetary offer on response times (CI = [− 0.070, 0.023]). The only significant regressor was stimulus repetition (CI = [− 0.262, − 0.147]): Participants were faster if the position of the odd one out on the current trial was identical to that on the previous trial. Longer offer durations preceding stimulus presentation made participants respond faster, but this effect was not statistically significant (CI = [− 0.042, 0.0003]). Figure 3 shows the regression coefficients and confidence intervals of all regressors.

Post hoc analysis of a slower subset of participants reveals a negative relationship between dopamine synthesis capacity in the nucleus accumbens and the effect of average reward rate on vigor.

As our participants were on average faster than the participants in the earlier studies ($p < 0.001$ for Guitart-Masip and $p = 0.094$ for Beierholm), we wondered whether the lack of effects could be accounted for by a ceiling effect. Given that our participants had volunteered for a multi-session pharmacological-PET/fMRI study (Hofmans et al. 2020; Westbrook

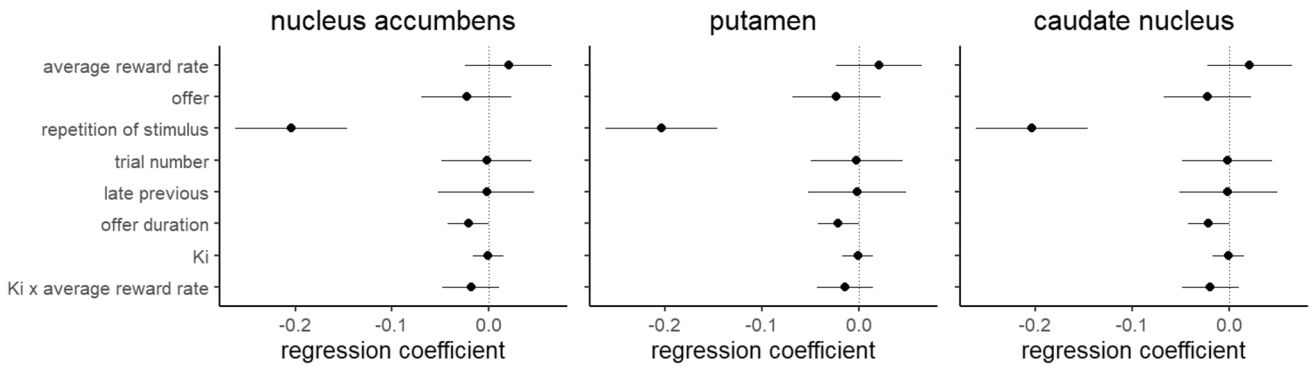

Fig. 3 Parameter estimates from the Bayesian multilevel model (fixed effects; model 1) on response time, based on data from the entire group ($N = 44$). Error bars represent 95% credible intervals

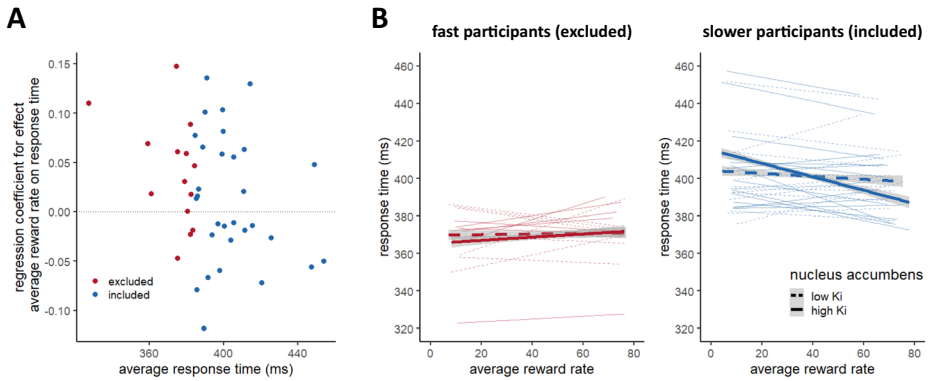

Fig. 4 **A** Relationship between average response time across all trials and the regression coefficient for average reward rate on response times (coefficient from model 0). Pearson's $r = -0.30$, $p = 0.045$. The fastest (red) participants are excluded from the subset, whereas the slower (blue) participants are included in the subset. **B** Relationship between average reward rate and response times for the faster, excluded, participants ($N = 14$) and the slower, included, participants ($N = 30$). The speeding effect of average reward rate appears stronger for participants with high versus low dopamine synthesis capacity, but only in the slower subset. Participants in each group are median-split based on dopamine synthesis capacity in the nucleus accumbens (for visualization only); a median-split based on the putamen or caudate nucleus gave qualitatively similar results. Grey shading around the thick line represents 95% confidence interval. Thin lines represent individual participants.

et al. 2020) and that it has been found that participants who volunteer for imaging studies have higher levels of cognitive motivation compared to those who volunteer for a simple behavioral study (Sayalı & Badre 2019), it could be expected that our participants were indeed more prone to ceiling effects on speed. In other words, it is possible that we did not observe any effects of average reward rate because a part of our participants could not perform any faster in response to a high average reward rate. This possibility is further suggested by the fact that only slower and not faster participants showed the expected individual variation in average reward rate effect on response time (Fig. 4A). To test this hypothesis, we subset our participants, retaining only our slower participants: We excluded the minimal number of participants, such that the group mean response time did not significantly differ ($p > 0.05$) anymore from that of Guitart-Masip et al. (2011). This resulted in a dataset including 30 participants with a mean participant-averaged response time of 404.6 ms (SD = 19.0 ms).[1] A reanalysis of this subset of slower participants revealed that the effect of average reward rate on response time varies as a function of dopamine synthesis capacity (Fig. 4B).

Upon reanalysis of this subset of data, we again found no main effect of average reward rate on response times (CI = [−0.051, 0.051]), but we did find a negative interaction between dopamine synthesis capacity in the nucleus accumbens and average reward rate. As hypothesized,

[1] Inferences were identical regardless of the exact procedure, including retaining only the 50% or 75% slowest participants, or retaining only the subsample of slower participants which most closely resembled that of the placebo group in Beierholm et al. (2013) in terms of response times ($N = 31$).

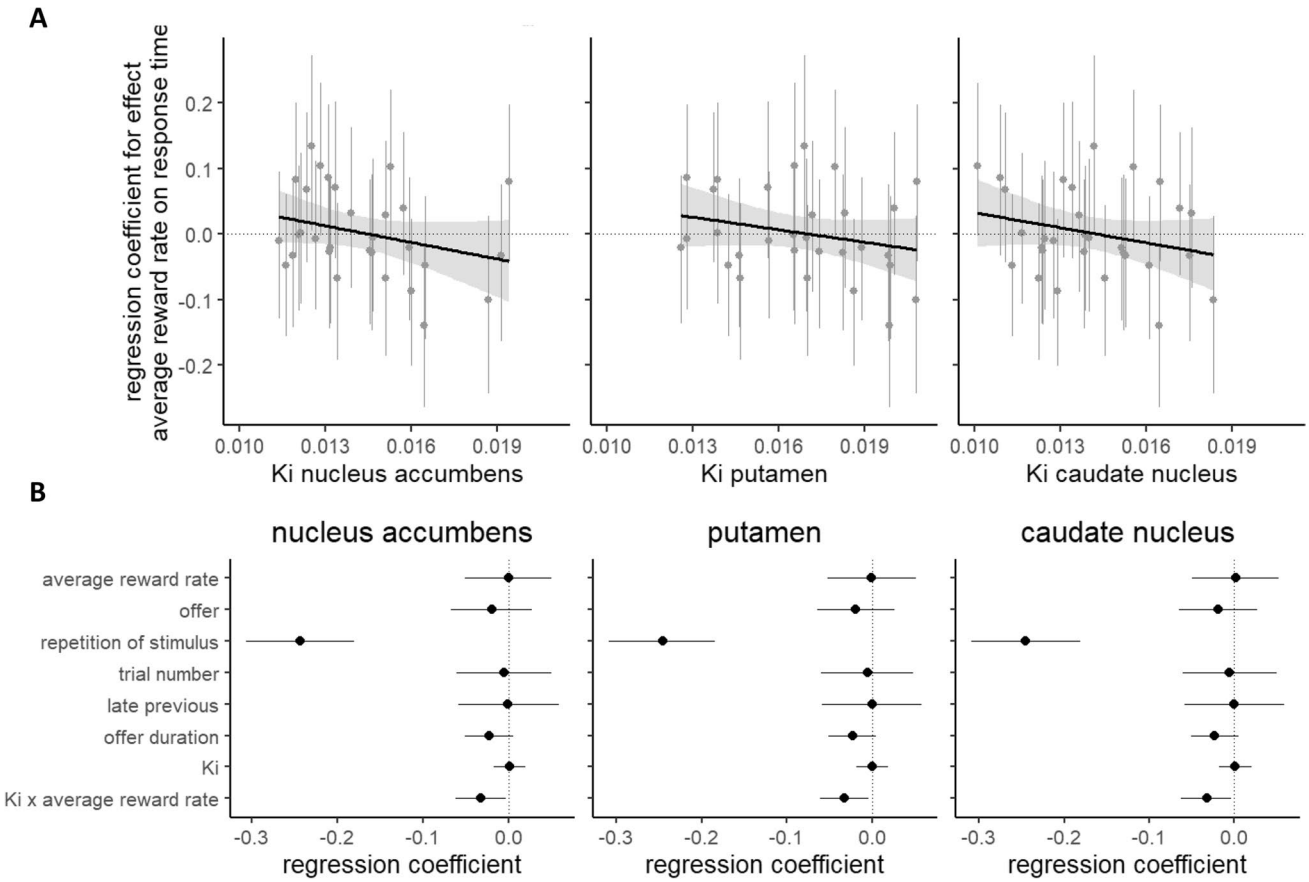

Fig. 5 Based on data from the slower subset ($N = 30$) **A** The effect of average reward rate on response times (*y*-axis) as a function of dopamine synthesis capacity (*x*-axis) in the nucleus accumbens (left), putamen (middle), and caudate nucleus (right). The effect of average reward rate on response times is indexed as the individual regression coefficient (sum of the fixed (group level) and random (individual) effects slopes) associated with average reward rate from the Bayesian multilevel model (excluding dopamine synthesis capacity; model 0). Error bars represent 95% credible intervals pertaining to the individual coefficients; grey shading represents 95% confidence interval around the regression line. **B** Parameter estimates from the Bayesian multilevel model (fixed effects) on response time, with dopamine synthesis capacity (K_i) interacting with average reward rate (model 1)

individuals with higher dopamine synthesis capacity showed a stronger invigorating effect of average reward rate (CI = [− 0.061, − 0.003]; Fig. 5A). Importantly, these effects could not be explained by group differences in dopamine synthesis capacity between the faster and slower participant group ($t = 0.99$, $p = 0.329$). Again, we found a significant negative effect of stimulus repetition (CI = [− 0.307, − 0.181]). No other regressors were significant (Fig. 5B).

Exploratory analyses reveal a similar negative relationship between dopamine synthesis capacity in both the putamen and caudate nucleus and the effect of average reward rate on vigor.

Exploratory analyses including K_i values extracted from our additional ROIs, the putamen and caudate nucleus, again showed no interaction between dopamine synthesis capacity and average reward rate (putamen: CI = [− 0.043, 0.014]; caudate nucleus: CI = [− 0.049, 0.010]). Figure 3 shows the regression coefficients and confidence intervals of all regressors.

Upon reanalysis of the slower participant subset, we found a negative interaction between striatal dopamine synthesis capacity and average reward rate, similar to the interaction effect between dopamine synthesis capacity in the nucleus accumbens and average reward rate: Individuals with higher dopamine synthesis capacity showed a stronger invigorating effect of average reward rate (putamen: CI = [− 0.061, − 0.004]; caudate nucleus: CI = [− 0.062, − 0.003]; Fig. 5).

Voxel-wise analysis qualitatively confirms the ROI-based results

Exploratory voxel-wise regression analyses qualitatively confirmed our ROI-based results. While we did not find a

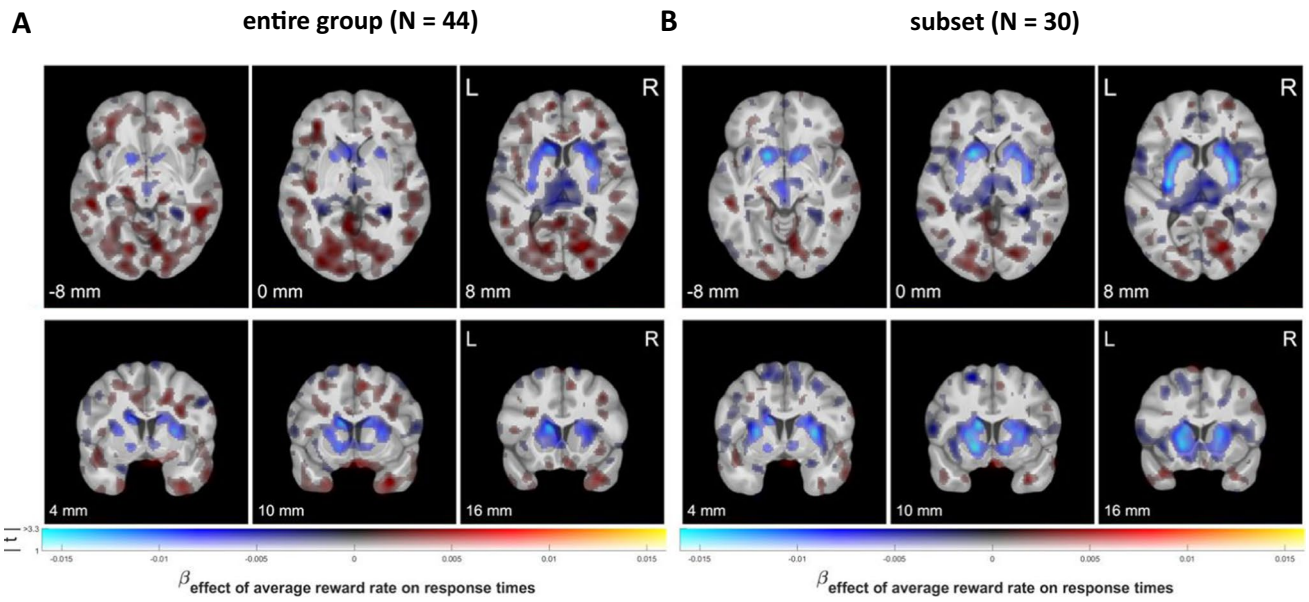

Fig. 6 Whole-brain regression weights of dopamine synthesis capacity predicted by the effect of average reward rate on response times. Left: based on data from the entire group (N = 44); Right: based on data from the slower subset (N = 30). The blue color indicates that individuals with higher dopamine synthesis capacity exhibit a stronger negative (i.e., invigorating) effect of average reward rate on response times; display format from (Zandbelt, 2017)

strong relationship between dopamine synthesis capacity and the effect of average reward rate on response times when analyzing the entire participant group (Fig. 6A), we did find a negative relationship when only analyzing the slower subset of participants (Fig. 6B): Individuals with higher striatal dopamine synthesis capacity showed a stronger invigorating effect of average reward rate.

Control analyses confirm a specific interaction between dopamine synthesis capacity in the nucleus accumbens and average reward rate

We then ran control analyses on data from the slower participant subset in which dopamine synthesis capacity interacted with all other regressors (model 2; Fig. 7A). In the nucleus accumbens, this still revealed a significant negative interaction between striatal dopamine synthesis capacity and average reward rate (CI = [− 0.103, − 0.005]). However, the interaction was not significant for the other two ROIs (putamen: CI = [− 0.078, 0.018]; caudate nucleus: CI = [− 0.083, 0.016]). No other interactions were significant. Thus, the interaction with dopamine synthesis capacity in the nucleus accumbens on vigor was specific to average reward rate.

To control for potentially confounding effects of age, sex, time delay between PET acquisition and behavioral testing, and tracer dose, we conducted additional control analyses including these variables as main effects and in interaction with average rate (model 3; Fig. 7B). This still revealed a significant interaction between dopamine synthesis capacity and average reward rate on response times (nucleus accumbens: CI = [− 0.074, − 0.006]; putamen: CI = [− 0.062, − 0.0009]; caudate nucleus: CI = [− 0.076, − 0.014]). No other interactions were significant. Thus, the interaction between dopamine synthesis capacity and average reward rate cannot be attributed to any of these potentially confounding variables.

No effect of offer on accuracy

We did not find an effect of offer on response times. We reasoned that the incentive structure of the task, in which participants would receive the reward upon correct completion of the trial as long as they responded within the time limit, might have emphasized accuracy over response times. We therefore ran additional analyses on the slower subset of participants, using models equivalent to the ones described above with dopamine synthesis capacity interacting with all predictors (model 2), but now with accuracy (correct or incorrect) as the dependent variable (with a Bernoulli family function). This revealed no significant effect of offer, either as a main effect (CI = [− 0.130, 0.200]) or in interaction with dopamine synthesis capacity (nucleus accumbens: CI = [− 0.150, 0.140]; putamen: CI = [− 0.162, 0.132]; caudate nucleus: CI = [− 0.119, 0.164). The only significant effect was that of stimulus repetition (CI = [0.523, 1.181]), with higher accuracy when the current stimulus set was the same as in the previous trial.

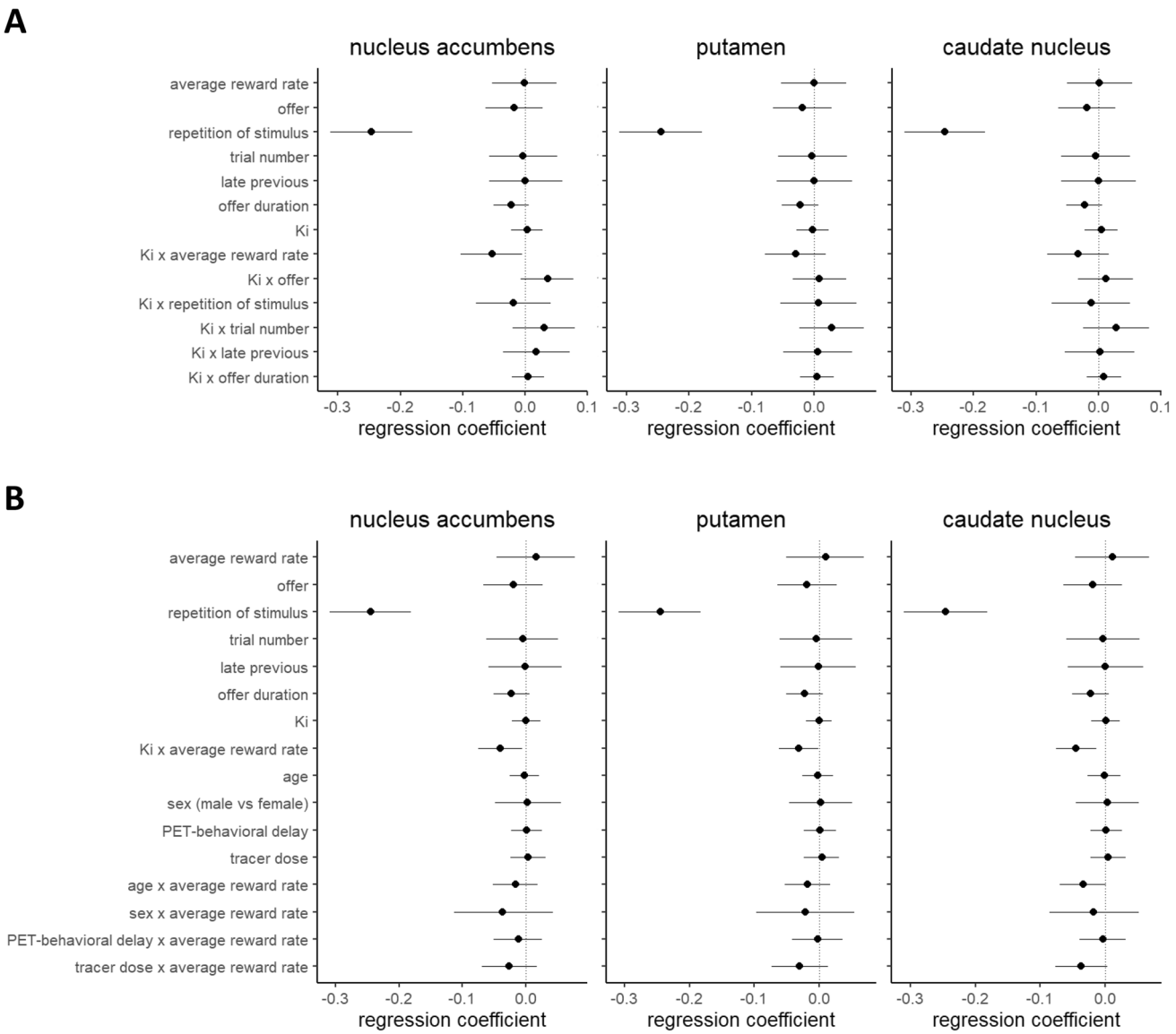

Fig. 7 Based on data from the slower subset ($N = 30$) **A** Parameter estimates from the Bayesian multilevel model (fixed effects) on response time, with dopamine synthesis capacity (K_i) interacting with all other regressors (model 2). **B** Parameter estimates from the Bayesian multilevel model (fixed effects) including control variables (model 3). Error bars represent 95% credible intervals

Table 1 Overview of the Bayesian mixed effects models

	Regressors
Model 0	Average reward rate + offer + repetition of stimulus + trial number + late previous + offer duration
Model 1	Average reward rate + offer + repetition of stimulus + trial number + late previous + offer duration + K_i + K_i * average reward rate
Model 2	Average reward rate + offer + repetition of stimulus + trial number + late previous + offer duration + K_i + K_i * average reward rate + K_i * offer + K_i * repetition of stimulus + K_i * trial number + K_i * late previous + K_i * offer duration
Model 3	Average reward rate + offer + repetition of stimulus + trial number + late previous + offer duration + K_i + K_i * average reward rate + age + sex + PET-behavioral delay + tracer dose + age * average reward rate + sex * average reward rate + PET-behavioral delay * average reward rate + tracer dose * average reward rate

Models 1–3 were performed separately for each of the three brain regions (K_i for either nucleus accumbens, putamen, or caudate nucleus).

Regressors additionally modeled as random effects per participant in each model: average reward rate + offer + repetition of stimulus + trial number + late previous + offer duration

Table 2 Mean behavioral responses and dopamine synthesis capacity of the entire group ($N = 44$) and the slower subset ($N = 30$)

	Entire group Mean (SD)	Slower subset Mean (SD)
Percentage of correct button presses	91.8 (4.2)	91.1 (4.7)
Percentage of rewarded trials	81.2 (8.6)	78.1 (8.7)
Percentage of too late trials	11.9 (6.7)	14.7 (6.4)
Percentage of wrong trials	6.9 (3.2)	7.3 (3.6)
Mean individual RT, all trials (ms)	394.6 (23.1)	404.6 (19.0)
Mean individual RT, rewarded trials (ms)	385.1 (18.6)	393.0 (14.9)
Mean individual RT, too late trials (ms)	484.0 (17.4)	486.9 (14.1)
Mean individual RT, wrong trials (ms)	367.0 (23.7)	374.5 (22.6)
Dopamine synthesis capacity, nucleus accumbens (K_i)	0.0145 (0.0020)	0.0143 (0.0022)
Dopamine synthesis capacity, putamen (K_i)	0.0170 (0.0023)	0.0168 (0.0025)
Dopamine synthesis capacity, caudate nucleus (K_i)	0.0141 (0.0021)	0.0141 (0.0022)

Discussion

We tested the hypothesis that participants with higher striatal dopamine synthesis capacity, particularly in the nucleus accumbens, exhibit a stronger invigorating effect of average reward rate. Across the entire group, we did not find this interaction between dopamine synthesis capacity and average reward rate, nor did we find a main invigorating effect of average reward rate. However, a post hoc split based on average individual response times, resulting in a subset of 30 participants with slower response times, revealed the predicted relationship, such that participants with higher striatal dopamine synthesis capacity exhibited a stronger invigorating effect of average reward rate. These findings are in line with the theory that dopamine signals the average reward rate, or the opportunity cost of sloth (Niv et al. 2007). This study builds on prior empirical work demonstrating a stronger effect of average reward rate after administration of the dopamine precursor L-dopa compared with placebo (Beierholm et al. 2013), by extending these findings to individual variation in striatal dopamine synthesis capacity, rather than pharmacologically induced states. Moreover, it extends the findings of Beierholm et al. (2013) by assessing subregions of the striatum, finding that the interaction between dopamine synthesis capacity and average reward rate is particularly present for the nucleus accumbens, in line with theorizing by Niv et al. (2007).

Interpreting our results warrants caution, because the final dataset included only 30 participants, which is a relatively low sample size to study individual differences. Moreover, the stratification into faster and slower participants was a post hoc decision. However, this decision was based on the notion that participants who were already very fast — and substantially faster than what was found in Guitart-Masip et al. (2011) and Beierholm et al. (2013) — could potentially not speed up even more, which was supported by the data showing that faster participants indeed rarely exhibited a negative effect of average reward rate. Moreover, we did not see the hypothesized main effect of average reward rate on vigor, which has been observed in earlier studies (Guitart-Masip et al. 2011; Beierholm et al. 2013; Hamid et al. 2016; Rigoli et al. 2016; Otto & Daw 2019). As we used the same average learning rate that was fitted on the Guitart-Masip et al. (2011) data in the current study and manipulated the available offer using the same pre-specified function, we remain agnostic as to why we did not find a main invigorating effect of average reward rate here.

Nevertheless, the current result does concur with previously established and replicated effects of within-subject changes in dopamine on motivation and vigor. The finding that the relationship between dopamine synthesis capacity and average reward rate on vigor remained significant only for the nucleus accumbens and not for the more dorsal regions of the striatum, after controlling for possible interactions between dopamine synthesis capacity and other predictors, dovetails prior observations. A considerable body of literature has implicated the nucleus accumbens in behavioral activation and vigor, demonstrating that (pharmacologically induced) increases in dopamine enhance activity, including response rates on a lever pressing task or wheel running, and dopamine depletion suppresses activity (Taylor & Robbins 1984, 1986; Sokolowski & Salamone 1998; for a review, see Salamone et al. 2016). Another series of studies, using acute dopamine precursor (phenylalanine/tyrosine) depletion to decrease dopamine synthesis capacity and transmission, found that reduced dopamine diminishes the drive to exert effort in return for various rewards, including tobacco, alcohol, and the opportunity to exercise, which was measured using a progressive ratio breakpoint task in which participants had to systematically increase their number of key presses for reward (Barrett et al. 2008; Venugopalan et al. 2011; O'Hara et al. 2016). Likewise, dopamine receptor blocking in the nucleus accumbens slowed cue-evoked movement initiation to approach a reward (du Hoffmann &

Nicola 2014). Consistent with a key role for the nucleus accumbens in linking reward and vigor are the findings of an fMRI study which showed that periods of high average reward rate, operationalized as blocks in which participants received a high relative to a low baseline reward rate in a visual search task, were associated with both increased vigor, indexed by the force exerted during button presses, and increased neural activation in the midbrain and the nucleus accumbens (Rigoli et al. 2016). Moreover, Hamid et al. (2016) provided a direct link between accumbens involvement in the effects of average reward rate on vigor in rats: Increases in dopamine release in the nucleus accumbens reflected a high average reward rate, which in turn had an invigorating effect on rats performing a trial-and-error choice task, an effect later replicated in Mohebi et al. (2019). Combined with fast-scan cyclic voltammetry (Hamid et al. 2016) and optical dLight sensors (Mohebi et al. 2019) to measure subsecond fluctuations in dopamine release, they additionally found that the correlation between dopamine release and average reward rate could best be described as dopamine signaling an average of rapidly evolving expectations of future reward, informed by the value of recent previous rewards (Berke 2018). Importantly, as this motivational signal could be observed across multiple timescales, ranging from subsecond to minute-by-minute fluctuations, rather than being inherently slow or tonic (Niv et al. 2007), it might indeed signal our trial-wise manipulation of average reward rate. Our current results support the above observations that assign a key role to the nucleus accumbens by showing that the relationship between dopamine synthesis capacity and average reward rate on vigor was particularly strong for the nucleus accumbens compared to the more dorsal putamen and caudate nucleus, underlining distinct cognitive and dopaminergic functionality in distinct striatal subregions (Westbrook et al. 2021).

Other studies have found discrepant results on dopamine's role in reward effects on vigor. For example, when participants had to squeeze a dynamometer in return for reward, administering L-dopa did not affect the force exerted by the participants, even though the exertion of more force meant that participants would finish the trial faster and could therefore complete more trials within a certain time period and earn more money (Zénon et al. 2016). It should be noted here that this study thus operationalized vigor as the amount of force exerted, rather than inverse response times. Another recent study showed mixed effects of rewards on vigor using a rewarded saccade task. When patients with Parkinson's disease, characterized by striatal dopamine depletion, were on their dopaminergic medication (compared to when off their medication), they showed greater response vigor, indexed as peak saccadic velocity residuals, for contingent rewards, whereas when participants were off their dopaminergic medication, they showed greater vigor for guaranteed rewards (Grogan et al. 2020). This suggests that when it is instrumental to be faster, dopamine boosts reward-related invigoration (see also Mikhael et al. 2021). However, a critical difference between these studies and the current study is that there was no manipulation of the average reward rate in the former, only of the immediate reward, thus not directly addressing the interaction between dopamine and average reward rate.

We did not find an effect of instantaneous offer on vigor nor accuracy. While this lack of effect of instantaneous offer is in line with earlier studies that have manipulated average reward rates in similar ways (Guitart-Masip et al. 2011; Beierholm et al. 2013; Otto & Daw 2019), it is still rather surprising given previous observations that incentives improve behavioral performance (Takikawa et al. 2002; Hübner & Schlösser 2010; Manohar et al. 2015). Perhaps the use of a slowly fluctuating offered amount, rather than a binary high versus low offer as is seen in many other studies, masked the potential effect of the current offer: A high average reward rate would be associated with a high expected value of the upcoming offer, which would attenuate a strong positive reward prediction error and its associated dopamine burst otherwise brought about by a high instantaneous offer, thereby blunting any observable effects of the latter.

As discussed above, there was a lack of an invigorating effect of average reward rate, particularly in the faster participants. A possible explanation might be that those individuals were following the task instructions very carefully and were committed to responding fast. This might be viewed as a rule-governed way of performing the task, leaving little room for a more experience-based effect of average reward rate on response times (Hayes 1989; Doll et al. 2009). Future studies using this task could test whether there is indeed a relationship between the effect of average reward rate, average response times, and the degree to which participants' behavior is driven by instruction versus experienced-based reinforcement (Doll et al. 2009).

Recent medication or drug use could influence dopaminergic signaling, thereby affecting our results. A limitation of this study is that participants did not receive urine drug screens to rule out recent substance use. Although participants were thoroughly screened before the [^{18}F]-DOPA PET study, including an interview about alcohol, cannabis, and other psychotropic drug use, and they were required (and agreed) to abstain from cannabis two weeks before the start of the [^{18}F]-DOPA PET study, and to abstain from alcohol 24 h, and psychotropic medication and recreational drugs 72 h before the PET session, we cannot rule out recent drug use before the behavioral test session or non-compliance. Another limitation of the study is the temporal disparity between PET scanning and behavioral testing, which could potentially obscure the link between behavior and neurochemistry. However, the test–retest reliability of our

assessment of dopamine synthesis capacity has been demonstrated to be satisfactory for our design (Egerton et al. 2010), and statistically controlling for this time delay showed that it did not affect the results.

In sum, we acknowledge the need for caution in interpreting the results and note that we did not find the predicted relationship between the invigorating effect of average reward rate and dopamine synthesis capacity across the entire group. However, post hoc analysis of a more sensitive subset of the dataset provides preliminary support for a role of individual variation in (ventral) striatal dopamine in the effects of average reward rate on vigor, thereby substantiating the literature on the mechanistic link between average reward rate, vigor, and dopamine. We think our current findings are worthy of replication in future studies, given the importance of unraveling computational mechanisms underlying individual differences in choice behavior for advancing psychiatry (Maia & Frank 2011; Collins & Frank 2014; Huys et al. 2021).

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Data availability The data and analysis scripts used in this article will be made publicly available after manuscript acceptance at the following web address: https://doi.org/10.34973/kb2p-j456. Prior to accessing and downloading the shared data, users must create an account. It is possible to use an institutional account or a social ID from Google, Facebook, Twitter, LinkedIn, or Microsoft. After authentication, users must accept the Data Use Agreement (DUA); after which, they are automatically authorized to download the shared data. The DUA specifies whether there are any restrictions on how the data may be used. The Radboud University and the Donders Institute for Brain, Cognition and Behaviour will keep these shared data available for at least 10 years.

Declarations

Conflict of interest The authors declare no competing interests.

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