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Effect of Striatal Dopamine on Pavlovian Bias. A Large [^{18}F]-DOPA PET Study

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Interaction between Pavlovian and instrumental control systems is key for adaptive motivated behavior, but also plays an important role in various neuropsychiatric disorders, including depression, addiction, and anxiety. Here, we employed the flouorodopa positron emission tomography ([^{18}F]-DOPA PET) in healthy participants ($N = 100$) to assess whether dopamine synthesis capacity (K_i), specifically in the ventral striatum, accounts for individual variation in Pavlovian-to-instrumental transfer (PIT). Surprisingly, this was not the case. Rather, the relationship of ventral striatal K_i with PIT depended on working memory (WM) capacity. Ventral striatal dopamine boosted the effects of Pavlovian cues on instrumental responding to a greater degree in participants with higher WM capacity. Caution is warranted to interpret this post hoc four-way interaction given the modest sample size. Nonetheless, these results chime with prior findings demonstrating that dopaminergic drugs boost Pavlovian biases to a greater degree in participants with greater WM capacity and highlight the importance of interactions between striatal dopamine and WM capacity.

Keywords: dopamine synthesis capacity, Pavlovian-to-instrumental transfer, working memory capacity, ventral striatum

Supplemental materials: https://doi.org/10.1037/bne0000547.supp

Adaptive behavior depends on the motivational control of action, which involves interactions between two key behavioral control systems (Dickinson & Balleine, 1994). A Pavlovian controller, which relies on classical Pavlovian conditioning (Pavlov, 2010), refers to the learning of *stimulus*-outcome contingencies, that is, learning to *predict* outcomes in the environment. Here, after a neutral stimulus has become associated with a valued outcome, the presentation of the neutral stimulus alone elicits the hardwired responses normally associated with the outcome itself. Conversely, the instrumental controller learns *response*-outcome contingencies, that is, learns *what actions to take* to obtain valued outcomes (Skinner, 2019). Thus, while both controllers shape behavior, instrumental, but not Pavlovian, control enables us to direct our actions toward the goals in the current environment. These controllers interact: hardwired Pavlovian conditioned responses affect instrumental goal-directed behavior, a phenomenon called Pavlovian-to-instrumental transfer (PIT). Usually that interaction is adaptive, for example, when appetitive Pavlovian biases prompt us to hurry up to buy the last lovely smelling bun from the bakery. However, there are situations in which Pavlovian responses are in

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Ping Chen played lead role in formal analysis, investigation, methodology, software, validation, visualization, writing of original draft and writing of review and editing. Dirk E. M. Geurts played supporting role in formal analysis, methodology, software and visualization and equal role in writing of review and editing. Jessica I. Määttä played lead role in data curation and project administration and supporting role in formal analysis, investigation, supervision and writing of review and editing. Ruben van den Bosch played supporting role in formal analysis, investigation, software and writing of review and editing and equal role in data curation. Lieke Hofmans played supporting role in writing of review and editing and equal role in data curation. Danae Papadopetraki played supporting role in writing of review and editing and equal role in data curation. Hanneke den Ouden played supporting role in formal analysis and investigation and equal role in methodology, supervision and writing of review and editing. Roshan Cools played lead role in conceptualization, funding acquisition, investigation, methodology, project administration, supervision and writing of review and editing, supporting role in visualization and equal role in formal analysis and writing of original draft.

All behavioral and PET data, as well as the analysis codes are stored in the Donders Institute data repository; DOI at https://doi.org/10.34973/mk1z-rs95 (Chen et al., 2022).

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conflict with context-appropriate instrumental responses, for example, when the need to hurry up for a meeting at work means we should avoid entering the bakery.

There is increasing evidence that different individuals vary greatly in the degree to which they exhibit Pavlovian biases of instrumental behavior. This variability has clinical relevance, because it accounts for individual variability in the vulnerability to relapse in alcohol dependence (Garbusow et al., 2014, 2016), recovery from depression (Huys et al., 2016) and personality disorder (Hallquist et al., 2018). However, the neurobiological mechanisms underlying this individual variation in Pavlovian biasing are unknown. While recognizing that a wider neural circuit including the amygdala (Prévost et al., 2012; Talmi et al., 2008) is likely involved, we here focus on the contribution of ventral striatal dopamine to individual differences in Pavlovian biasing of instrumental control. We measure this bias with the classic PIT paradigm, which enables separate measurement of the distinct component processes of instrumental learning, Pavlovian conditioning and PIT in different stages (Huys et al., 2011).

The focus on ventral striatal dopamine is based on observations that Pavlovian cues elicit dopamine release in the ventral striatum (VS; Flagel et al., 2011; Wassum et al., 2011). Moreover, dopaminergic drug administration enhances appetitive Pavlovian boosting of instrumental approach behavior in both experimental rodents (Dickinson et al., 2000; Wassum et al., 2011; Wyvell & Berridge, 2001) and human volunteers (Hebart & Gläscher, 2015; Soutschek et al., 2020; Swart et al., 2017). Furthermore, the impact of Pavlovian biases on rodent instrumental behavior has been shown to be reduced by pharmacological blockade of dopamine D1 and D2 receptors (Lex & Hauber, 2008), and selective lesions of the ventral striatum (Hall et al., 2001). Clinically, Pavlovian bias-related blood-oxygen-level-dependent signals detected in functional magnetic resonance imaging in the ventral striatum predict alcohol intake and relapse in alcohol-dependent patients (Garbusow et al., 2016). Together, this prior work led us to hypothesize that individual variability in Pavlovian-to-instrumental interaction depends on individual differences in dopamine function in the ventral striatum. Specially, we hypothesized that participants with higher dopamine levels would show stronger Pavlovian biasing.

To test this hypothesis, we combine measurements of dopamine transmission using the flouorodopa positron emission tomography ([^{18}F]-DOPA PET) imaging with behavioral quantification of individual PIT effects. Uptake of the radiotracer [^{18}F]-DOPA indexes the degree to which dopamine is synthesized in the striatal terminals of midbrain dopamine neurons, thus contributing to stable individual differences in striatal dopamine release (Veronese et al., 2021). Most previous work with PET imaging has used relatively small samples, precluding robust conclusions about individual differences. To increase the statistical power for detecting reliable between-subject effects, we investigated a large sample of 100 volunteers.

Finally, based on previous work (Geurts et al., 2022; Swart et al., 2017) showing that effects of methylphenidate, a nonspecific catecholamine (dopamine and noradrenaline) reuptake blocker, on Pavlovian biasing depended on working memory (WM) capacity, as measured with the listening span (Daneman & Carpenter, 1980), we explored the possibility that effects of interindividual variability in dopamine function are uncovered only if we take WM capacity into account. Specifically, results from both previous studies (Geurts et al., 2022; Swart et al., 2017) demonstrated that methylphenidate promotes (appetitive and aversive) Pavlovian biasing of instrumental behavior, to a greater degree in those individuals with higher WM capacity. These findings chime with further extensive prior evidence for a link between dopaminergic drug effects and WM capacity (Cools & D'Esposito, 2011), previously suggested to be a putative proxy of dopamine synthesis capacity (K_i; Cools et al., 2008; Landau et al., 2009). We therefore include WM capacity in our secondary analyses to investigate whether K_i effects depend on variability in WM capacity.

Method and Materials

General Procedure

The data reported here were acquired in the context of a larger pharmacological PET/fMRI study, components of which have been and will be reported separately (Hofmans et al., 2020, 2022; Määttä et al., 2021; van den Bosch, Hezemans, et al., 2022; van den Bosch, Lambregts, et al., 2022; Westbrook et al., 2020; an overview of the complete study at https://osf.io/d3h8e). For this study, participants paid five visits. The [^{18}F]-DOPA PET scan and the PIT task (Figure 1) were performed on the final visit (day 5). On their first visit (day 1), participants were screened for eligibility, in part based on medical and psychiatric interviews, and completed assessments of WM capacity; listening span (Daneman & Carpenter, 1980; Salthouse & Babcock, 1991), digit span (Groth-Marnat et al., 2000), and crystallized intelligence (Crawford et al., 1989; Schmand et al., 1991), and also providing measures of spontaneous eye blink rate (electrooculography), and an anatomical brain scan. The screening session was followed by pharmacological-fMRI sessions on day 2–4, which are reported elsewhere (van den Bosch, Lambregts, et al., 2022). On the final visit, in addition to the PIT task, participants completed a second Digit Span Test and a fluid intelligence assessment; Wechsler Adult Intelligence Scale, 4th edition, Dutch edition (Wechsler, 2008), followed by an [^{18}F]-DOPA PET scan to establish participants' K_i. Participants received participation fee of €319 upon completion of the full study. The financial compensation for participating in this study is determined as follows: Participants received €172 for the behavioral sessions (€8 per hr × 6 hr × 3 sessions, + 3 hr intake, + 0.5 hr at home). For the fMRI sessions, they received an extra fee of €2 per hour (€2 × 1 hr × 3 sessions, + 0.5 hr during intake). For the administration of medicines, they received an extra reimbursement of €30 (€10 × 3 sessions). For the PET scan, they received €100. Finally, for the extra saliva sample and computer tasks at home (1 hr), they received an extra €10.

Transparency and Openness

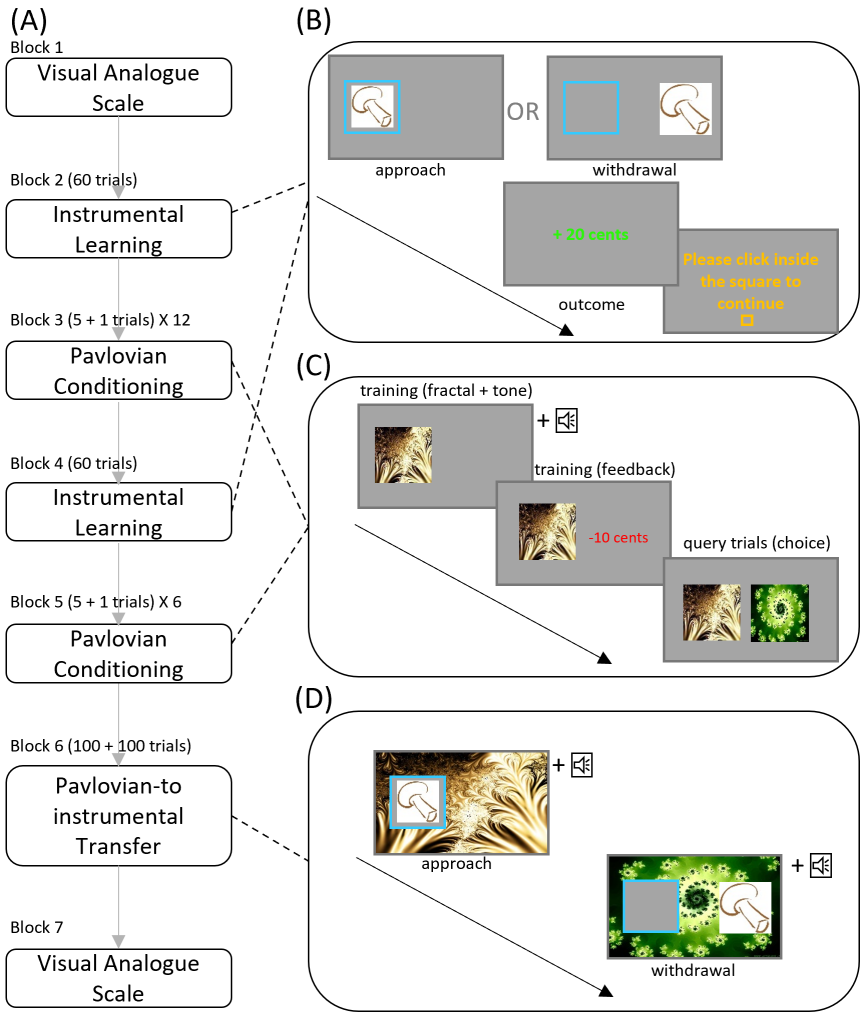
All behavioral and PET data, as well as the analysis codes are stored in the Donders Institute data repository; DOI at https://doi.org/10.34973/mk1z-rs95 (Chen et al., 2022).

Participants

A total of 100 healthy participants (aged 18–43, $M \pm SD$, 22.96 ± 5.04; 50 men) were recruited in this study. All participants were native Dutch speakers, right-handed, with normal or corrected-to-normal vision and hearing, and no history of psychiatric or neurological disorders (for further exclusion

Figure 1

Illustration of the Pavlovian-to-Instrumental Transfer Task



Note. (A) Flowchart of the seven blocks in the task. (B) Instrumental learning stage. In the approach context, participants were asked to click inside the blue square to pick up a good mushroom, or do nothing for the bad mushroom. In the withdrawal context, participants were asked to do nothing to keep a good mushroom, or to click the blue square to throw away the bad mushroom. Each response is followed by an outcome (e.g., 20 cents). Participants had to click the orange square to continue to the next trial. (C) Pavlovian conditioning stage. Participants were trained to learn the stimulus-outcome associations observing the presented fractal and tone followed by a feedback prompt (e.g., −10 cents). After every five trials of training, there would be a query trial, where participants were asked to choose the fractal with the higher value. (D) Pavlovian-to-instrumental transfer stage. Participants completed the instrumental learning task again with the Pavlovian fractals as background, in both approach and in withdrawal action context. See the online article for the color version of this figure.

criteria, see Supplemental Methods). Written informed consent was obtained from each participant. Ethical approval was acquired from the regional research ethics committee (Commissie Mensgebonden Onderzoek, region Arnhem-Nijmegen; 2016/2646; case number: NL57538.091.16).

Eight participants were excluded for the following reasons: no PET scan obtained ($N = 1$), drop-out ($N = 4$), software malfunction led to data loss ($N = 3$). Ten participants were excluded because of poor performance (Supplemental Methods). Data from 82 participants were included in the analyses reported here.

PIT Task

The PIT task was established to be sensitive to appetitive and aversive Pavlovian biases of instrumental behavior (Geurts et al., 2013b; Huys et al., 2011). The task (Figure 1A) comprised three stages: (a) instrumental learning, (b) Pavlovian conditioning, and (c) transfer. The task took around 30 min to complete.

In the instrumental learning stage, participants were instructed that they had to maximize gains and minimize losses by collecting good mushrooms, while avoiding bad mushrooms. They had to

learn by trial and error which mushrooms were good or bad. The instrumental training stage (Figure 1B) consisted of two blocks: one approach and one withdrawal block (order A-W or W-A counterbalanced). In the approach block, participants could collect mushrooms by clicking inside a blue square (go) or avoid mushrooms by doing nothing (no-go). In the withdrawal block, another set of mushrooms were presented. In this block, participants were now instructed to "throw away" bad mushrooms by clicking inside the blue square (go) or do nothing to collect the mushroom (no-go). For both good and bad mushrooms, correct (go or no-go) responses were mostly rewarded, and incorrect responses were mostly punished. Reward and punishment contingencies were probabilistic (75%). Each block comprised 60 trials and lasted approximately 3 min. On each trial, the mushroom stimulus was presented, and subjects had to respond before it disappeared in 1.5 s. The blue square turned red for 0.5 s if participants clicked inside the box. They then saw the monetary outcome (gain or loss of −100, −10, 0, +10, +100 cents) for 0.8 s. The outcome appeared after 1.5 s if no response was recorded. Participants initiated the next trial by clicking on a square in the middle of the screen. For approach trials, a blue square is presented around the mushroom, and contralateral to the mushroom on withdrawal trials. The mushroom stimuli-to-condition assignment was counterbalanced across participants.

The Pavlovian conditioning stage (Figure 1C) comprised conditioning and query trials. On each of ninety conditioning trials, a compound Pavlovian stimulus consisting of a fractal and a tone was presented for 1 s and were followed deterministically with monetary reward or loss (+100, +10, 0, −10, −100) for 2 s. After every five training trials, a query trial was presented, where two fractals were shown, and participants had to choose the fractal with higher value out of the two presenting fractals (no time limit). The fractal stimuli-to-condition assignment was counterbalanced across participants. To assess the effect of Pavlovian conditioning on subjective valuation, a Visual Analogue Scale (VAS) was used to measure participants' subjective preference of the five fractals. Before and after conditioning, participants rated each of the five fractals and clicked with the mouse on a scale anchored with "not nice at all," "neutral" and "very nice." The position of the mouse click was extracted and used to compute its proportion of the scale.

In the PIT stage (Figure 1D), participants were presented with the same instrumental stimuli (mushrooms) as during instrumental learning and were instructed to continue to make the learned go/no-go responses. Critically, these instrumental stimuli were presented together with the Pavlovian conditioned fractal cues, and responses were not followed by monetary outcomes: the PIT stage was performed in extinction. Action-specific PIT effects were defined as modulation of the tendency to go by the interaction of action context factor (approach and withdrawal) and the Pavlovian cue value (+100, +10, 0, −10, −100). The order of approach and withdrawal blocks were counterbalanced across participants. Each contained 100 trials.

[^{18}F]-DOPA PET K_i

K_i measurements were obtained using a Siemens positron emission tomography/Computed Tomography scanner at the Department of Nuclear Medicine of Radboudumc. Details of PET acquisition, preprocessing, T1 acquisition, and region selection are reported in the Supplemental Methods. Briefly, dynamic PET images were obtained over 89 min. K_i was defined as the rate of conversion of [^{18}F]-DOPA into dopamine, which is indexed as the tracer influx rate K_i (min^{-1}). Average K_i values were extracted from three striatal regions of interest (ROIs) in subjects' native image space: the ventral striatum, the caudate nucleus, and the putamen. These ROIs were defined based on functional parcellation of an independent resting state fMRI dataset, using a *k*-means clustering algorithm (Piray et al., 2017).

WM Capacity Measure of Listening Span

During the Listening Span Test of WM capacity (Daneman & Carpenter, 1980), participants listen to a series of sentences and answer a multiple-choice question about each sentence. After each series (increasing from one to seven), they are asked to recall the last word of each sentence. The listening span score was recorded as the total number of words they wrote down in the right order. Two raters scored the results independently; the listening span score used in the analysis here was the average score of both raters (interrater reliability, Cronbach's $\alpha = .98$).

Digit Span

For completeness, we also report, in the Supplemental Results, effects as a function of the averaged digit span (Groth-Marnat et al., 2000) collected on both the intake session and the PET session. Participants hear sequences of numbers and have to repeat them. Digit span has two phases, one phase that requires the participant to repeat them in the order they heard it, called forward span, and another phase that requires them to repeat the numbers they heard backward, called backward span.

Data Analysis

Analyses of Instrumental Learning and Pavlovian Conditioning

Accuracy in the instrumental learning stage (correct/incorrect) was assessed using mixed-effect logistic regression modeling with action context and trial number as within-subject variables, and ventral striatal K_i, and listening span as between-subject variables. The action context was coded as a categorical variable; while the trial number, K_i, and listening span were coded as continuous variables and were mean-centered. Specially, the equation we used was "Choice ~ Action × Trials × VS × Span + (1 + Action × Trials | Individual)." A mixed-effect model of proportion choice of the higher value option on the Pavlovian query trials included the difference in value between the two fractals (value_diff) and trial number as within-subject variables and ventral striatal K_i and listening span as between-subject variables. The value_diff was coded as the mean-centered absolute difference between two fractals' ranking (value_diff: −1.5, −0.5, 0.5, 1.5). The equation we used was "Choice ~ Value_Diff × Trials × VS × Span + (1 + Value_Diff × Trials | Individual)." Type III Wald χ^2 tests were performed to extract the p values (the probability of obtaining the observed estimate).

Analyses of Subjective Preferences

To investigate whether participants' subjective preference of the background fractals changed after Pavlovian conditioning, we used

a linear mixed-effect model including valence (appetitive, neutral and aversive) and time (pre-, postconditioning) as within-subject variables and ventral striatal K_i and listening span as between-subject variables. The liking rating measured by the VAS score was used as the dependent variable. Specially, the equation we used was "VAS ~ Valence × Time × VS × Span + (1 + Valence| Individual)."

Analyses of Action-Specific PIT

Probability of go responses from the critical PIT phase of the task were analyzed with mixed-effect logistic regressions with a full random effect structure of intercept and slope. Predictors included action context (two levels: approach and withdrawal) and valence (three levels: appetitive, neutral, aversive). The dependent variable was the binomial response (go or no-go).

As in our previous studies using this paradigm, the valence comprised three levels (aversive, neutral, appetitive), given previous observations (Garbusow et al., 2014, 2016; Geurts et al., 2013a, 2013b; Geurts et al., 2022; Huys et al., 2011) that valence sign, but not magnitude, of the Pavlovian cue differentially affected PIT. Thus, we combined high appetitive (+100 points) and low appetitive (+10 points) Pavlovian cues in one level, and equivalently high aversive (−100 points) and low aversive (−10 points) in one level.

To test our key hypothesis that the PIT effect varies as a function of individual variation in ventral striatal K_i, we added the between-subject variable K_i values from the ventral striatal ROI. To explore whether such effects might depend on WM capacity, we also added listening span as a second between-subject variable. Specially, the equation we used was "Choice ~ Action × Valence × Span × ROI + (1 + Action × Valence | Individual)."

To explore whether any effects of dopamine and/or WM capacity on PIT are accompanied by effects on Pavlovian conditioning; for example, stimulus-reward learning (Flagel et al., 2011); and/or instrumental learning (de Boer et al., 2019) itself, we ran supplementary mixed-effect models of choices from the Pavlovian stage and the instrumental stage completed prior to the PIT stage, which also included the variables VS-K_i and listening span (Supplemental Results; Table S2). Specially, the equation we used for Pavlovian conditioning was "Correct Choice ~ Action × Trials × VS × Span + (1 + Action × Trials | Individual)"; for instrumental learning we used "Correct Choice ~ Value_Diff × Trials × VS × Span + (1 + Value_Diff × Trials | Individual)."

Results

Participants Exhibited Instrumental Learning

Logistic mixed-effects modeling of accuracy on choice trials of the instrumental learning stage (Figure 2A) revealed a main effect of trial number ($\chi^2 = 71.6$, $p = .001$), demonstrating that participants successfully learnt to make the accurate response in order to maximize reward and minimize punishment across trials. There was no interaction between trial number and action context ($\chi^2 = 0.8$, $p = .4$), nor a main effect of action context ($\chi^2 = 0.8$, $p = .4$), indicating that there was no significant difference between learning to approach and to withdraw.

Participants Exhibited Pavlovian Conditioning

Logistic mixed-effects modeling of choice on the query trials of the Pavlovian conditioning stage revealed a main effect of trial number on probability of choosing the highest value stimulus: ($\chi^2 = 16.3$, $p = .001$), evidencing the presence of learning the Pavlovian associations between the conditioned stimuli (CSs; the fractals) and value (number of points). There was a main effect of the variable "difference in value" ($\chi^2 = 19.1$, $p = .001$), indicating higher proportion choice of the higher value option for fractal pairs with greater difference in value (Figure 2B). There was no "Trial number × Differences in value" interaction ($\chi^2 = 0.1$, $p = .8$), indicating no significant differences in learning the Pavlovian associations across time.

Participants' subjective preferences of the fractals, as indexed by the liking ratings (Figure 2C), changed after Pavlovian conditioning. Linear mixed-effects modeling of participants' liking ratings revealed that Pavlovian conditioning affected liking ratings differentially for the appetitive, neutral and aversive CS (Valence × Time: $\chi^2 = 101.3$, $p = .001$, Figure 2C). This was because the simple main effect of valence was much greater after conditioning ($\chi^2 = 187.0$, $p = .001$). Participants expressed similar liking for all fractals before conditioning ($\chi^2 = 0.1$, $p = .9$). After Pavlovian conditioning, the liking ratings significantly decreased for aversive fractals ($\chi^2 = 59.6$, $p = .001$) but increased for appetitive fractals ($\chi^2 = 35.8$, $p = .001$). No differences were detected for neutral fractals ($\chi^2 = 0.2$, $p = .7$). These changes in the VAS scores after the conditioning stage indicates successful Pavlovian conditioning procedure.

Participants Showed Action-Specific Pavlovian-to-Instrumental Effect

In the critical PIT stage, previously established basic task effects were replicated by mixed-effect models showing an action-specific PIT effect: while appetitive cues enhanced instrumental approach and suppressed withdrawal, aversive cues enhanced withdrawal and suppressed approach (interactive effect of Action × Valence on probability of go: $\chi^2 = 4.7$, $p = .03$, Figure 2D). Breakdown of the omnibus interaction revealed that there was a significant effect of Pavlovian conditioning on the instrumental actions (approach vs. withdrawal) when comparing appetitive with aversive ($\chi^2 = 5.0$, $p = .025$); but not when comparing aversive with neutral ($\chi^2 = .4$, $p = .1$) or appetitive with neutral ($\chi^2 = 1.8$, $p = .2$).

No evidence for an Effect of K_i on PIT

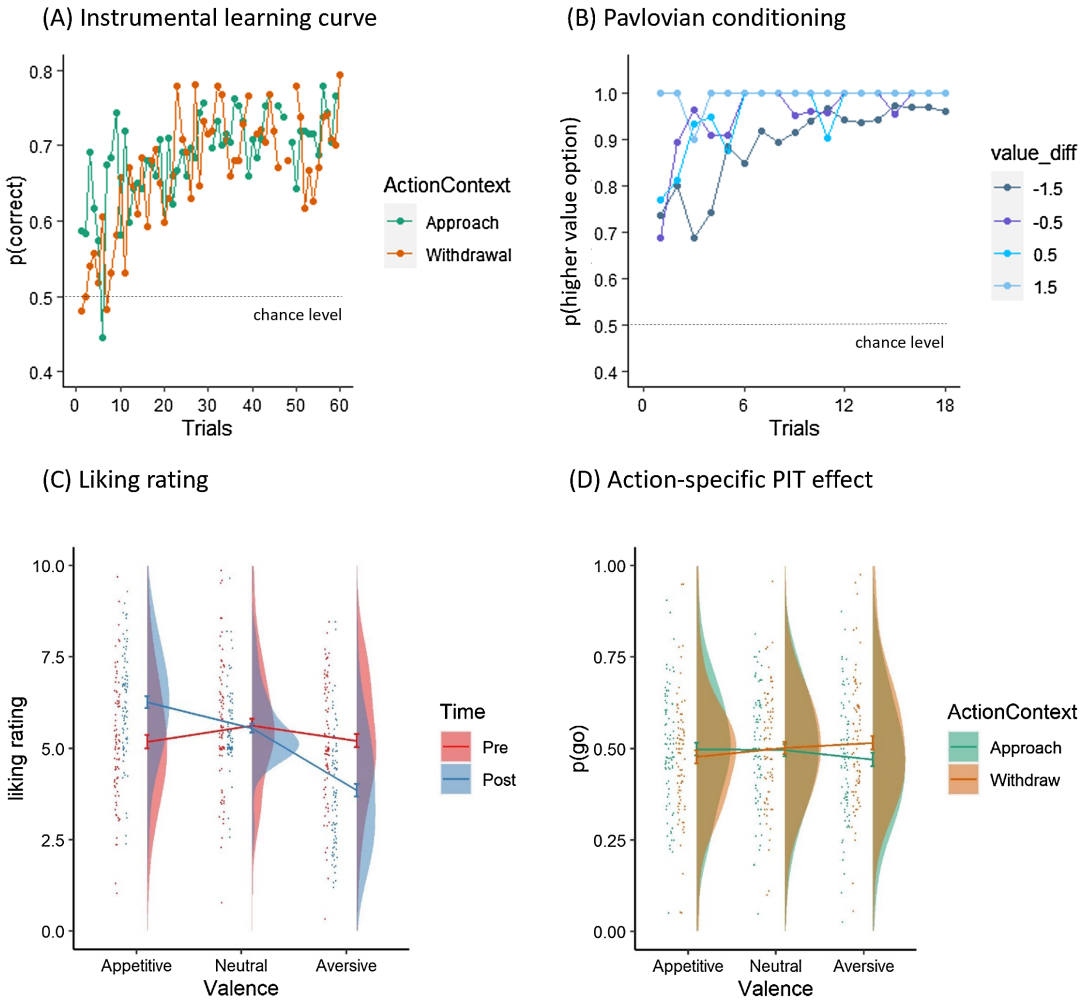
In contrast to our hypothesis, the PIT effect did not vary significantly with ventral striatal K_i (Valence × Action context × K_i in ventral striatum: $\chi^2 = 2.8$, $p = .1$; Valence × K_i in ventral striatum: $\chi^2 = 0.7$, $p = .4$). Exploration of the effects of K_i in the other striatal regions also revealed no effects (Valence × Action context × K_i in caudate nucleus: $\chi^2 = 0.6$, $p = .4$; putamen $\chi^2 = 0.5$, $p = .5$; Valence × K_i in caudate nucleus: $\chi^2 = 0.1$, $p = .7$; putamen: $\chi^2 = 0.1$, $p = .8$).

Effects of Ventral Striatal Dopamine on PIT Depended on WM Capacity

Individual differences in ventral striatal K_i positively predicted the PIT effect to a greater degree in participants with greater

Figure 2

Performance on the Instrumental Learning, Pavlovian Conditioning and Pavlovian-to-Instrumental Transfer Phases of the Task Across Individuals



Note. (A) Data from the instrumental learning stage. Average proportion of correct responses increased across trials, demonstrating that participants learned the instrumental task in approach and in withdrawal contexts. (B) Choice data from the Pavlovian conditioning stage. Averaged proportion choice of the higher value option (requiring participants to indicate which of two fractals that differed in value is higher) increased across trials, demonstrating that participants learned the value of the conditioned stimuli and can choose the one with higher value. (C) Liking rating before and after Pavlovian conditioning. Participants liked all the fractals better before (red) than after (blue) conditioning. Jittered points represent raw data, lines connect mean values and violin plots visualize probability density of the data distribution. For visualization purpose only, the VAS score in the probability scale was multiplied by 10. (D) Data from the Pavlovian-to-instrumental transfer stage. In the approach action context (green), average proportion of go responses was higher to appetitive than aversive cues, while in the withdrawal context (orange), the opposite effect was observed. VAS = Visual Analogue Scale. See the online article for the color version of this figure.

listening span (Figure 3A), reflected by a significant four-way interaction between VS-K_i, listening span, action context, and Pavlovian valence ($\chi^2 = 4.8$, $p = .029$).

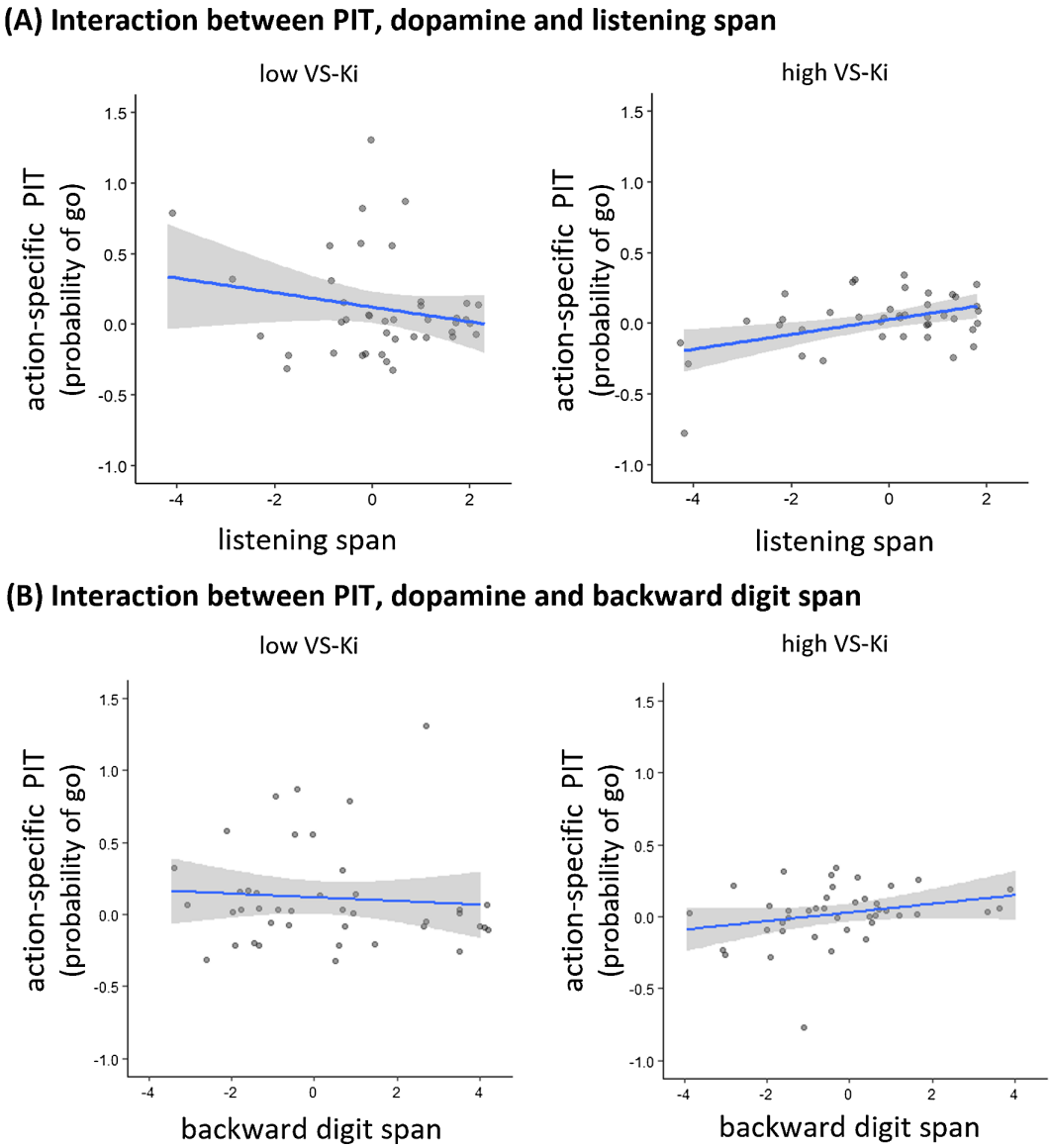
The effects of ventral striatal dopamine on PIT were conceptually robust in the sense that they were present also as a function of a different WM capacity measure, backward digit span (VS-K_i × Action Context × Pavlovian Valence × Backward Span: $\chi^2 = 4.3$, $p = .037$, Figure 3B).

No evidence for Effects of WM and K_i on Instrumental Learning and Pavlovian Conditioning

There was no significant effect of ventral striatal K_i on choice accuracy during instrumental learning, where learning is indexed by increased performance as a function of K_i (Action Context × Trial Number × VS-K_i: $\chi^2 = 0.1$, $p = .8$) or as a function of listening span (Action Context × Trial Number × Listening Span × VS-K_i: $\chi^2 = 1.3$,

Figure 3

Interactive Effects Ventral Striatal Dopamine Synthesis Capacity and Working Memory Capacity on Action-Specific Pavlovian-to-Instrumental Transfer (PIT)



Note. Participants with high, but not low ventral striatal dopamine synthesis capacity (VS-K_i) exhibited a positive effect of working memory capacity on PIT. This was the case when working memory capacity was measured by the listening span (A) and the backwards digit span (B). The *x*-axes represent working memory capacity measured with the listening span (A) or the backward digit span (B); the *y*-axes represent the degree of action-specific PIT, quantified as the probability of go responses on approach versus withdrawal trials in the presence of appetitive versus aversive Pavlovian cues: action-specific PIT effect = (pGoAppetitiveApproach—pGoAversiveApproach)—(pGoAppetitiveWithdrawal—pGoAversiveWithdrawal). PIT = Pavlovian-to-instrumental transfer; VS = ventral striatum. See the online article for the color version of this figure.

$p = .2$). This indicates that the span-dependent effect of K_i on PIT is unlikely to reflect span-dependent effects of K_i on instrumental learning.

There were no effects of K_i on the query trials during the Pavlovian conditioning stage. Here, we take the difference in the changed performance (number of trials across time) to select the highest valued stimulus in each presented pair, as a successful conditioning. There was no evidence for interactions between VS-K_i and trial number ($\chi^2 = 0.1, p = 1$), or between VS-K_i, trial number and value_difference ($\chi^2 = 0.1, p = .8$). There were neither effects of K_i that depended on listening span (VS-K_i × Listening Span × Trial Number: $\chi^2 = 0.2, p = .6$; VS-K_i × Listening Span × Value_diff × Trial Number: $\chi^2 = 0.9$,

$p = .3$). Regarding the other measure of conditioning, the pre–post liking ratings of the fractals (VAS scores), these did not differ with either K_i or listening span. There were no significant interactions between VS-K_i, valence (appetitive, neutral, aversive) and time (pre- vs. postconditioning; $\chi^2 = 0.1$, $p = .8$) or between VS-K_i, listening span, valence, time ($\chi^2 = 1.6$, $p = .2$). This indicates that the span-dependent effect of K_i on PIT is unlikely to reflect effects on Pavlovian conditioning, or the strength of the Pavlovian value associated with the CSs.

Finally, to investigate whether our key span-dependent effects of K_i on PIT can be accounted for by changes in the memory of instrumental values, learnt during the instrumental learning phase, we added to the mixed model, the probability of a go action in the last five trials for each stimulus extracted from the first instrumental learning stage (InstPgo). There was no significant effect of a five-way interaction (Action × Valence × K_i × WM × InstPgo, $\chi^2 = 0.3$, $p = .6$), but there was a main effect of InstPgo ($\chi^2 = 100.6$, $p = .001$), verifying the generalization of learned behavior to the PIT stage. That means if a participant consistently made a go for a certain stimulus (e.g., a purple mushroom), this behavior was carried over to the PIT stage.

Discussion

We investigated whether individual variability in Pavlovian biasing of instrumental responding can be accounted for by variation in K_i in the ventral striatum, measured with [^{18}F]-DOPA PET. This hypothesis was based on accumulating evidence from studies implicating a role for dopamine in the ventral striatum in PIT (Halbout et al., 2019; Lex & Hauber, 2008, 2010; Peciña & Berridge, 2013; Salamone et al., 2015; Wassum et al., 2013; Wyvell & Berridge, 2000, 2001). We found that while participants showed action-specific PIT, K_i did not predict individual variance in PIT. Instead, the effect of ventral striatal K_i on PIT depended on WM capacity: K_i interacted with WM capacity to predict (appetitive and aversive) PIT in participants. Specifically, participants with higher ventral striatal K_i showed greater PIT proportional to WM capacity.

Our findings are tantalizingly reminiscent of recent findings from three different psychopharmacological studies that have all demonstrated that dopaminergic drug effects on Pavlovian biasing of instrumental behavior depend on WM capacity (Geurts et al., 2022; Soutschek et al., 2020; Swart et al., 2017). Given previous results from PET studies showing a positive correlation between K_i and WM capacity (Cools et al., 2008; Landau et al., 2009), these interactive effects of dopaminergic drugs and WM capacity have often been interpreted as reflecting dependency on baseline levels of dopamine (Cools & D'Esposito, 2011). However, in the current sample, surprisingly, there was no correlation between K_i and WM capacity (Supplemental Figure 4). This discrepancy may be caused by the use of a different radiotracer for measuring K_i than in prior studies ([^{18}F]-DOPA rather than ^{18}F-fluoromethyl-tyrosine [^{18}F]-FMT). Specifically, while both F-DOPA and FMT ligands are substrates for aromatic amino acid decarboxylase, [^{18}F]-DOPA is subject to additional in vivo metabolism, implying lower signal-to-noise ratio than [^{18}F]-FMT (DeJesus et al., 1997), and perhaps also to some degree reflecting dopamine turnover rather than synthesis capacity (Dejesus et al., 2001). Future work is required to reconcile the growing body of literature demonstrating differential, sometimes even contrasting effects of K_i measured with FMT and F-DOPA (Berry et al., 2016, 2018; Cools et al., 2008; Dejesus et al., 2001; Ito et al., 2011; Kumakura et al., 2010; van den Bosch, Hezemans, et al., 2022). While this lack of effect might reflect the use of a different radiotracer, this observation does imply that an account in terms of baseline dependency is less plausible. Furthermore, while a dopamine proxy account would predict additive effects of K_i and WM capacity, here, we observe an *interactive* effect. Therefore, the present finding is more in line with the alternative proposal that baseline span-dependency of drug effects reflect instead fundamental interactions between distinct forms of behavioral control. Specifically, recent evidence indicates that reinforcement learning efficacy can depend on the degree to which participants rely on WM strategy with distinct reinforcement learning and WM controllers implicating dopamine in the striatum and prefrontal cortex, respectively (Collins et al., 2017; Collins & Frank, 2012).

Why would effects of ventral striatal K_i on PIT depend on WM capacity? One possibility is that, depending on WM capacity, participants adopted different learning strategies during the instrumental learning stage of the task. Indeed, prior research has demonstrated that reinforcement learning tasks can be completed successfully by reliance on fast and capacity-limited WM mechanisms often associated with the prefrontal cortex, rather than by relying on slow, cumulative learning mechanisms, often associated with the basal ganglia (Collins & Frank, 2012). For example, that prior work has revealed significant set size effects on accuracy in an instrumental learning task that required participants to choose between different actions for various numbers of stimuli. In our study, higher span participants might have relied more readily on a WM and less on a classic reinforcement learning strategy (Collins & Frank, 2012). Stronger reliance on a reinforcement learning strategy allows action values to be cached, possibly rendering them more robust to subsequent distractions or biases. Perhaps the use of a WM strategy during instrumental learning led the learnt action values of high-span participants to become more vulnerable to dopamine-dependent Pavlovian biases, elicited during the subsequent PIT phase. The present experiment does not allow us to test this possibility, because accuracy during the instrumental learning phase might reflect adequate use of either a WM or a reinforcement learning strategy. Future work is required to test this speculative hypothesis, for example, using a novel design that allows assessment of PIT effects as a function of WM load (e.g., set size) manipulation during a preceding instrumental learning stage (Collins & Frank, 2012).

One aim of the present study was to investigate the valence-specificity of the effect of K_i on PIT. This was inspired by prior evidence for a more pronounced role of dopamine in appetitive than aversive contexts (Boureau & Dayan, 2011; Cools et al., 2011; Guitart-Masip, Duzel, et al., 2014; Guitart-Masip, Economides, et al., 2014; Guitart-Masip et al., 2011, 2012; Mirenowicz & Schultz, 1996), as well as controversy on this valence-specificity (Bromberg-Martin et al., 2010; Lloyd & Dayan, 2016; van Nuland et al., 2020). However, contrary to these theories and empirical findings implying a more prominent role of dopamine in appetitive contexts, breakdown analyses of the interaction between K_i, WM and PIT showed that this interaction was mainly driven by the aversive rather than the appetitive condition. While this discrepancy requires confirmation in future work, this observation is more in line with studies that emphasize intact dopamine levels are also necessary for behavioral aversion (Fadok et al., 2009; Ventura et al., 2007).

Previously, we have established that administration of the nonspecific catecholaminergic drug methylphenidate altered both appetitive and aversive Pavlovian biases as measured using the same paradigm (Geurts et al., 2022), as well as a related task (Swart et al., 2017). In summary, these results are not in support of the hypothesis that effects of dopamine on instrumental action are solely, or even more strongly, present in appetitive Pavlovian contexts.

Finally, we note some words of caution, when interpreting the current results. First, the lack of a strong effect of K_i on PIT does not undermine previous studies implicating a role for ventral striatal dopamine transmission in PIT (Halbout et al., 2019; Lex & Hauber, 2008, 2010; Peciña & Berridge, 2013; Wassum et al., 2013; Wyvell & Berridge, 2000, 2001). Dopamine levels in the brain are a function not only of K_i, but also of the sensitivity and availability of dopamine receptors, dopamine transporters and the degree of dopamine release. Thus individual variability in PIT might well reflect variation in dopamine receptor availability (de Boer et al., 2019; Soutschek et al., 2020), dopamine transporter density or dopamine release (Berry et al., 2018), and genetic variability of the dopaminergic system (Richter et al., 2014). Consequently, a link between individual differences in dopamine and PIT might still be readily revealed when employing other PET tracers, or when perturbing the dopamine system. Second, the observed interaction of WM capacity and K_i with PIT represents a high-level four-way interaction involving two between-subject factors and is thus more vulnerable to overfitting than is a lower order interaction. Although the sample size of this study is large compared with other dopamine PET studies, it is still relatively small for reliable quantification of the size of such a four-way interaction. This positive predictive value of this four-way interaction should be assessed in future confirmatory replication work. Third, future studies are required to establish the test–retest reliability of the key measures under the present study here. Prior [^{18}F]-DOPA PET imaging research (Egerton et al., 2010) has indicated that the reliability of [^{18}F]-DOPA uptake is high across two scan sessions (intraclass correlation coefficients: 0.68–0.94). WM capacity estimates with the listening span and digit span have also been reported to be stable (Pearson's correlation of backward digit span across 2 days: $r = .6$, $p = .001$; backward span and listening span: $r = .4$, $p = .001$). However, test–retest reliability of our key PIT metric has not been addressed previously. Nevertheless, an analysis of split-half reliability of the Key Valence × Action Effect in our sample suggests adequate stability across the two halves of the instrumental mushroom stimulus set ($r = 0.7$, $p = .001$). Finally, the behavioral PIT effect in the current sample was smaller compared with the original study (Huys et al., 2011) using the same paradigm. This may have resulted from the stricter subject exclusion rules compared with earlier studies. Specifically, ten participants were excluded because of deterministic behavior to the Pavlovian stimuli, that is, we excluded the participants with the strongest behavioral PIT effects, because for such deterministic behavior we cannot exclude that participants did not misunderstand the task. Moreover, these excluded participants might have adopted a higher order cognitive strategy such as explicit WM based tracking of past outcomes. This is particularly likely given that the Pavlovian outcome was the same as the instrumental outcome (i.e., money) in the present study. Some of the Pavlovian bias observed here might well reflect a more explicit rule-based memory mechanism than the classic associative Pavlovian bias expressed in animals. Future studies will be needed to establish whether the link with WM capacity and ventral striatal dopamine is also present for outcome-general (rather than outcome-specific) forms of PIT, where Pavlovian and instrumental outcomes are not the same (Corbit & Balleine, 2011, 2015; Prévost et al., 2012). For example, prior work has demonstrated that outcome-specific and outcome-general PIT invoke distinct neural mechanisms (Corbit & Balleine, 2005, 2011; Corbit et al., 2001; Lex & Hauber, 2008; Prévost et al., 2012; Talmi et al., 2008).

Conclusion

In contrast to our prediction, there was no association between individual differences in striatal K_i and Pavlovian biasing of instrumental behavior. Instead, the effect of K_i on Pavlovian biasing depended on WM capacity. While this effect should be interpreted with caution, it concurs with recent pharmacological work evidencing interactive effects of dopaminergic drugs and WM capacity, highlighting the complexity of the role of K_i on PIT.

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