doi:10.1093/brain/awy341 BRAIN 2019: 142; 719–732 | 719

BRAIN
A JOURNAL OF NEUROLOGY

Dopamine restores cognitive motivation in Parkinson's disease

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Disorders of motivation, such as apathy, are common in Parkinson's disease, and a key feature of such disorders is a greater aversion to effort. In humans, the experience of cognitive effort is ubiquitous, and cognitive apathy has traditionally been considered distinct and separable from other subtypes. Surprisingly, however, the neurobiology of cognitive motivation is poorly understood. In particular, although dopamine has a well-characterized role in incentivizing physically effortful behaviour, a critical, unresolved issue is whether its facilitatory role generalizes to other domains. Here, we asked how dopamine modulates the willingness of patients with Parkinson's disease to invest cognitive effort in return for reward. We tested 20 patients with idiopathic Parkinson's disease across two counterbalanced sessions—ON and OFF their usual dopaminergic medication—and compared their performance to 20 healthy age-matched controls. We applied a novel task in which we manipulated cognitive effort as the number of rapid serial visual presentation streams to which participants had to attend. After training participants to ceiling performance, we then asked them to choose between a low-effort/low-reward baseline option, and a higher-effort/higher-reward offer. Computational models of choice behaviour revealed four key results. First, patients OFF medication were significantly less cognitively motivated than controls, as manifest by steeper cognitive effort discounting functions in the former group. Second, dopaminergic therapy improved this deficit, such that choices in patients ON medication were indistinguishable from controls. Third, differences in motivation were also accompanied by independent changes in the stochasticity of individuals' decisions, such that dopamine reduced the variability in choice behaviour. Finally, choices on our task correlated uniquely with the subscale of the Dimensional Apathy Scale that specifically indexes cognitive motivation, which suggests a close relationship between our laboratory measure of cognitive effort discounting and subjective reports of day-to-day cognitive apathy. Importantly, participants' choices were not confounded by temporal discounting, probability discounting, physical demand, or varying task performance. These results are the first to reveal the central role of dopamine in overcoming cognitive effort costs. They provide an insight into the computational mechanisms underlying cognitive apathy in Parkinson's disease, and demonstrate its amenability to dopaminergic therapy. More broadly, they offer important empirical support for prominent frameworks proposing a domain-general role for dopamine in value-based decision-making, and provide a critical link between dopamine and multidimensional theories of apathy.

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Keywords: dopamine; Parkinson's disease; apathy; cognitive effort; decision-making

Abbreviations: DAS = Dimensional Apathy Scale; RSVP = rapid serial visual presentation

Received July 4, 2018. Revised November 6, 2018. Accepted November 7, 2018. Advance Access publication January 24, 2019
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Introduction

From students to professionals, the willingness to engage in cognitively demanding tasks is central to human behaviour. In the extreme case, an aversion to effort is a hallmark of motivational disorders, and is particularly common in diseases of dopaminergic dysfunction (Chong and Husain, 2016; Salamone and Correa, 2018). In particular, ~40% of patients with Parkinson's disease experience disorders of motivation (den Brok *et al.*, 2015), and a subset of these are thought to experience a unique form of 'cognitive apathy' that is distinct from other subtypes (Levy and Dubois, 2006; Pagonabarraga *et al.*, 2015). Dopamine is known to play a crucial role in motivating individuals to invest physical effort in return for reward, and many prominent frameworks suggest that this effect should generalize to other domains of effort (Cools, 2015; Verguts *et al.*, 2015; Westbrook and Braver, 2016). However, the neurobiology of cognitive apathy remains poorly understood, and the key prediction that dopamine plays a domain-general role in motivation remains untested.

A hallmark of apathy is its multidimensionality, and putative classifications have distinguished cognitive apathy from other subtypes, such as its 'auto-activation' (i.e. physical) and 'emotional-affective' forms (Levy and Dubois, 2006). This distinction has been validated by recent questionnaire-based tools developed specifically to probe parkinsonian apathy along these dimensions [e.g. the Dimensional Apathy Scale (DAS); Radakovic and Abrahams, 2014; Santangelo *et al.*, 2017]. Although neurophysiological data on cognitive effort-based decisions are scarce, emerging data provide neural evidence in favour of such a distinction. Cross-species studies have shown that cognitive effort is processed by dissociable neuroanatomical substrates, with the amygdala emerging as a key node in a network that uniquely encodes cognitive effort costs in rodents (Hosking *et al.*, 2014) and humans (Chong *et al.*, 2017). Interestingly, the only study to have directly examined the effect of dopamine on cognitive effort showed that dopamine antagonism in rodents did not affect the willingness of animals to invest cognitive effort in return for rewards (Hosking *et al.*, 2015). These data suggest that cognitive effort may devalue rewards in a manner distinct from other effort costs.

Such findings contrast with current theories of dopamine function, many of which predict that dopamine plays a more general role in motivation, by incentivizing effort regardless of the domain in which it is experienced (Cools, 2015; Verguts *et al.*, 2015; Westbrook and Frank, 2018). This prediction has been elaborated by a recent account of cognitive effort, which proposed that dopamine may mediate cognitive motivation through two separate mechanisms—by facilitating the investment of effort itself, and enhancing working memory processes (Westbrook and Braver, 2016). Indirect evidence for a domain-general representation of effort costs comes from neuroimaging studies, which have shown that effort in both the cognitive and physical domains are represented across a core network of common areas. Notably, this network includes the striatum (Schmidt *et al.*, 2008; Schouppe *et al.*, 2014), as well as areas with which it is heavily interconnected, such as the medial prefrontal cortex (Chong *et al.*, 2017). To date, however, the prediction that dopamine plays a causal role in facilitating human cognitive effort-based decisions has not been empirically tested.

A recent successful approach to studying human motivation has been to frame it in a neuroeconomic context (Westbrook and Braver, 2015; Chong *et al.*, 2016; Pessiglione *et al.*, 2017). Such approaches typically require participants to decide how much effort they are willing to trade-off for a given reward (Czernecki *et al.*, 2002; Schmidt *et al.*, 2008; Chong *et al.*, 2015; Massar *et al.*, 2018). Participants' decisions can then be computationally modelled as a function of the subjective value that individuals assign to rewards that have been devalued by the effort required to obtain them ('effort discounting'). This approach has several strengths. First, there is substantial evidence that subjective value is represented in the striatum (Kable and Glimcher, 2009; Peters and Büchel, 2010), which makes it a sensitive measure of disordered decision-making caused by dopaminergic dysfunction. Second, subjective value represents a direct input to a prospective decision, and can therefore be used as a direct measure of the cost of effort. Third, it allows us to capture the individual differences that are inherent in cost–benefit decision-making, and may therefore have diagnostic utility, by providing an objective marker of individual apathy. Applying such models to cognitive effort-based decision-making therefore offers a promising approach to uncovering the dopaminergic mechanisms that underlie cognitive apathy.

Here, we tested the hypothesis that dopamine is critical to cognitive effort-based decision-making. We used a novel cognitive effort discounting task that manipulated effort in terms of divided attention. On each trial, participants were required to choose between a low-effort/low-reward baseline option, and a high-effort/high-reward offer. To examine the effects of disease and treatment on cognitive motivation, we tested patients over two sessions—ON and OFF their usual dopaminergic treatment—and compared their choices to those of healthy, age-matched controls. Our key questions were whether patients with Parkinson's disease were less cognitively motivated than controls, and, if so, whether and how dopamine therapy ameliorates these deficits. To address these issues, we first examined the frequency that the more effortful offer was accepted over the baseline option, and then focused on computationally modelling the subjective value of cognitively effortful offers.

Materials and methods

Participants

We recruited 20 patients with idiopathic Parkinson's disease, and an equivalent number of age- and gender-matched controls. Patients were recruited from clinical and community referrals, with the assistance of local support groups (Parkinson's Victoria), under approval by the local ethics committee. All patients had a diagnosis of idiopathic Parkinson's disease confirmed by at least one neurologist (T.C., D.T.), and were ON dopaminergic therapy with levodopa and/or dopamine agonists. Exclusion criteria included a history of concurrent neurological disease. Disease severity was assessed with the Unified Parkinson's Disease Rating Scale (UPDRS). Controls had no history of neurological or psychiatric disease.

Apathy was assessed on the DAS (Radakovic and Abrahams, 2014). The DAS specifically probes motivation along three separate dimensions: 'Executive', 'Emotional', and 'Behavioural'. These subscales correspond to the 'Cognitive', 'Emotional-affective', and 'Auto-activation' subtypes originally postulated by Levy and Dubois (2006). Our patient sample captured a range of apathy scores (10–49), with 12/20 patients scoring in the apathetic range, based on a proposed cut-off score of >28.5 (Santangelo *et al.*, 2017). Of the DAS subscales, patients were more apathetic than controls on the Executive and Emotional, but not the Behavioural, subscales (Table 1).

To examine the effect of dopamine on motivation, patients were tested across two separate sessions: ON and OFF medication. For the ON session, patients were instructed to take their dopaminergic medication according to their usual regimen. During the OFF sessions, patients were tested following overnight withdrawal. ON and OFF sessions were counterbalanced across patients, and occurred at the same time of day, separated by ~2 weeks. To ensure that there were no practice effects or changes in strategy across sessions, performance in controls was also compared across two identical sessions separated by the same interval.

Procedure

Each session was divided into two phases (Fig. 1). In an initial reinforcement phase, participants were trained to perform each level of cognitive effort to ceiling performance, to ensure that they could be positively reinforced on every trial at every effort level (Fig. 1A and B). This was followed by the key choice phase, during which participants were asked to indicate their preference between a low-effort/low-reward baseline option, and a high-effort/high-reward offer (Fig. 1C). Stimuli were delivered through Presentation software (Neurobehavioral Systems), and presented on a laptop monitor positioned ~60 cm from participants and at a refresh rate of 60 Hz. Responses were registered on a Cedrus button-box.

Table 1 Summary of participant demographics

	Controls	Parkinson's disease	Group difference
n	20	20	N/A
Age, years	61.1 (13.6)	67.1 (9.1)	$t(38) = 1.64$, $P = 0.11$
Gender, M:F	12:8	12:8	$\chi^2 = 0.0$, $P = 1.0$
DAS[a] total	21.1 (8.07)	30.2 (9.83)	$U = 86$, $Z = 3.07$, $P = 0.002$
Executive ('cognitive')	4.4 (2.72)	8.65 (4.08)	$U = 76$, $Z = 3.34$, $P = 0.001$
Emotional ('emotional-affective')	7.65 (3.22)	10.3 (2.94)	$U = 117.5$, $Z = 2.25$, $P = 0.024$
Behavioural ('auto-activation')	9.1 (4.62)	11.2 (4.49)	$U = 160.5$, $Z = 1.07$, $P = 0.29$
Beck Depression Inventory[b]	3.55 (4.13)	9.5 (4.98)	$U = 71.5$, $Z = 3.49$, $P < 0.001$
MoCA Score[c]	28.1 (1.37)	27.7 (1.92)	$t(38) = 0.75$, $P = 0.45$
UPDRS[d]			
Section I	N/A	11.7 (6.61)	N/A
Section II	N/A	11.4 (6.39)	N/A
Section III	N/A	27.3 (18.1)	N/A
Section IV	N/A	2.2 (2.4)	N/A
Hoehn and Yahr stage[d]	N/A	1.37 (0.81)	N/A
Disease duration, years	N/A	5.4 (4.9)	N/A
Levodopa equivalence[e], mg	N/A	741.8 (564.3)	N/A
Interval between sessions, days	15.3 (4.95)	16.3 (8.17)	$t(38) = 0.44$, $P = 0.66$
Mean duration since last dose, h	N/A	ON: 1.58 (1.18) OFF: 14.0 (4.38)	N/A

Values are presented as mean (SD). N/A = not applicable.

[a]Proposed apathy cut-off score > 28.5 (Santangelo *et al.*, 2017). The Executive, Emotional and Behavioural subscales (Radakovic and Abrahams, 2014) correspond to the Cognitive, Emotional-Affective and Auto-activation subscales of Levy and Dubois, respectively (Levy and Dubois, 2006).

[b]Normal range: 1–16, low; 17–30, moderate; >31, severe.

[c]Montreal Cognitive Assessment (MoCA) normal range 26–30.

[d]Clinical severity was assessed with the UPDRS (Fahn *et al.*, 1987), and the modified Hoehn and Yahr scale. Scores on the motor section (Part III) are from the ON session.

[e]Levodopa equivalence doses (LED) were calculated based on standard formulae (Tomlinson *et al.*, 2010). Patients were on levodopa ($n = 5$), dopamine agonists ($n = 4$), or combinations of both ($n = 11$).

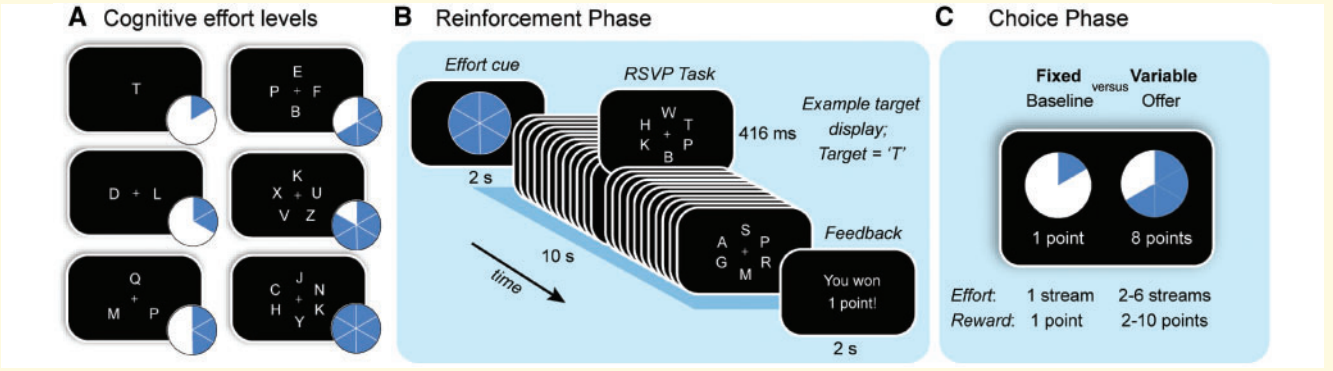

Figure 1 The Cognitive Effort Task. (**A**) Sample displays. Cognitive effort was manipulated as the number of RSVP streams (one to six) that had to be monitored for a target letter 'T'. Each level of effort was cued by a corresponding pie chart, here superimposed diagrammatically on sample displays. (**B**) In an initial reinforcement phase, participants were trained on each level of the cognitive effort task. Trials began with a cue indicating the number of streams to be monitored in that trial (here, six streams). This was followed by the task itself, which required participants to monitor the corresponding number of rapidly-changing letter streams for a target stimulus ('T'; example target display extracted). Participants received feedback at the end of each trial. (**C**) In the key choice phase, participants choose between a fixed low-effort/low-reward baseline (monitoring one stream for one point), and a variable high-effort/high-reward offer (monitoring two to six streams for 2, 4, 6, 8 or 10 points).

Reinforcement phase

Participants were first familiarized with the cognitive effort task (Fig. 1A). We used a rapid serial visual presentation (RSVP) design, in which cognitive effort was operationalized as the number of streams that participants had to monitor (1 to 6) for a target stimulus (the letter 'T') over a 10-s period. Letter stimuli were displayed in Arial 26-point font. The least effortful condition required participants to monitor a single stream of rapidly changing letters presented at fixation. In more effortful conditions, between two and six streams were positioned equiangularly and equidistantly (~1.5°) from fixation. Importantly, the duration of all trials, regardless of effort level, was held constant (10 s), ensuring that effort requirements were not confounded with time-on-task.

At the beginning of each trial, participants were cued with the number of letter streams they had to monitor on that trial (Fig. 1B). This cue appeared in the form of a pie chart, with the number of slices of pie indicating the number of streams to be presented. Each trial then consisted of the rapid serial visual presentation of 24 stimulus displays, each of which lasted 416 ms in duration, for a total trial length of 10 s. Participants were required to indicate by button press the appearance of the target letter, which could appear in any of the displayed streams (randomly determined). Targets appeared at pseudorandom temporal intervals, with the constraint that they could not appear at consecutive time points (to avoid an attentional blink). At the conclusion of each trial, participants were provided with feedback on their performance in the form of a reward outcome. They were rewarded with 1 point if they were able to complete each trial above a threshold level of performance (more than one hit; fewer than three false alarms); otherwise, they were rewarded with 0 points. Participants were instructed that their task was to maximize their points won, but were informed that these rewards were fictive.

Participants completed 60 trials in total (10 per effort level) to familiarize themselves with task requirements. These trials were divided into two blocks, with an opportunity to rest in-between. The order of effort levels was randomized. These were preceded by a practice block of 12 trials (two per effort level), which was not analysed. To verify that increasing the number of RSVP streams was effective in modulating the subjective perception of effort, we administered the mental demand subscale of the NASA Task Load Index, a 21-point visual analogue scale of cognitive effort (Hart and Staveland, 1988).

Choice phase

On each trial of the key choice phase, participants were presented with two combinations of effort and reward, and were asked to choose which was preferable to them (Fig. 1C). One option was a fixed, low-effort/low-reward baseline, which was the option to perform the lowest amount of effort (monitoring a single RSVP stream) for the lowest number of points (1). The alternative was a variable, high-effort/high-reward offer, which was the option to perform a greater amount of effort (monitoring two to six streams) for an increasing number of points (2, 4, 6, 8, 10). Note that the effort and reward levels of the variable offer were varied parametrically and independently, and the entire space of effort/reward combinations was sampled evenly and randomly over 100 trials. Trials were self-paced.

Participants were explicitly told that their decisions were hypothetical, in that points did not alter their remuneration, nor would they have to perform any of their choices. Rather, they simply had to consider the value of the high-effort/high-reward offer relative to the low-effort/low-reward baseline. This approach avoided issues associated with fatigue from having to perform each choice, as well as issues with changes in strategy associated with multiple testing sessions. We note

that previous studies have not reported reliable differences between potentially real and purely hypothetical rewards when making cost-based decisions (Johnson and Bickel, 2002; Madden *et al.*, 2003, 2004; Frank *et al.*, 2004; Bickel *et al.*, 2009; Chong *et al.*, 2015; Skvortsova *et al.*, 2017).

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Reinforcement phase: RSVP task performance

Increasing cognitive load with increasing effort

First, we verified that our attentional manipulation was effective in increasing cognitive load (Fig. 2A). Behavioural performance for each effort level was quantified as d' [i.e. $Z(\text{Hits}) - Z(\text{False alarms})$]. Extreme values of 1 (for hit rates) or 0 (for false alarm rates) were corrected with a log-linear approach (Hautus, 1995). Control performance for all measures in the reinforcement phase did not differ across Sessions 1 and 2, and was therefore collapsed.

The effect of disease on performance was analysed with an ANOVA on the factors of Group (Parkinson's disease OFF, controls) and Effort (Levels 1–6). Both main effects were significant, indicating a decrease in d' with increasing effort, and overall better performance in controls relative to Parkinson's disease OFF medication, with a non-significant interaction [Group, $F(1,38) = 6.71$, $P = 0.001$; Effort, $F(5,190) = 41.1$, $P < 0.001$; interaction, $F(5,190) = 1.10$, $P = 0.37$]. The comparison of Parkinson's disease ON versus control subjects yielded the identical result, showing a reduction in d' with increasing effort, and that patients, despite being ON medication, continued to have lower target detection sensitivities relative to controls [Group, $F(1,38) = 6.96$, $P = 0.01$; Effort, $F(3.6,138) = 39.3$, $P < 0.001$; interaction, $F(3.6,138) = 0.14$; $P = 0.96$]. In keeping with these findings were the results of a within-patients Drug × Effort ANOVA, which showed that their target detection sensitivities were similar regardless of whether they were ON or OFF drug [Drug, $F(1,19) = 0.34$, $P = 0.57$; Effort, $F(5,95) = 25.9$, $P < 0.001$; Drug × Effort, $F(5,95) = 1.43$, $P = 0.22$].

In sum, target detection sensitivity was poorer in patients, regardless of medication state, compared to controls. Supplementary analyses demonstrated that the decrement in performance in both groups was driven by lower hit rates, rather than higher false alarm rates (Supplementary material). Overall, the decrement in performance with increasing RSVP streams confirmed the effortful nature of the manipulation.

Reinforcement rates were constant across both groups in both sessions

Despite the decrement in performance with increasing load, we wished to ensure that participants could still perform each level so as to be reinforced on the majority of trials (Fig. 2B). Reinforcement rates were computed as the proportion of trials that participants were successfully rewarded at each level of effort. Notably, there were no differences between control and patient performance, nor were there any differences within patients as a function of drug [Parkinson's disease OFF versus controls: Group, $F(1,38) = 1.63$, $P = 0.21$; Effort, $F(3.1,119) = 0.89$, $P = 0.45$; interaction, $F(3.1,119) = 0.21$, $P = 0.90$; Parkinson's disease ON versus controls: Group, $F(1,38) = 2.90$, $P = 0.10$; Effort, $F(2.7,103) = 1.78$, $P = 0.16$; interaction, $F(2.7,103) = 0.57$, $P = 0.62$; Parkinson's disease ON versus Parkinson's disease OFF: Drug, $F(1,19) = 0.68$, $P = 0.42$; Effort, $F(2.8,53) = 1.04$, $P = 0.38$; interaction, $F(3.1,60) = 0.61$, $P = 0.62$]. Together, this indicates that reinforcement rates were equivalent across controls and

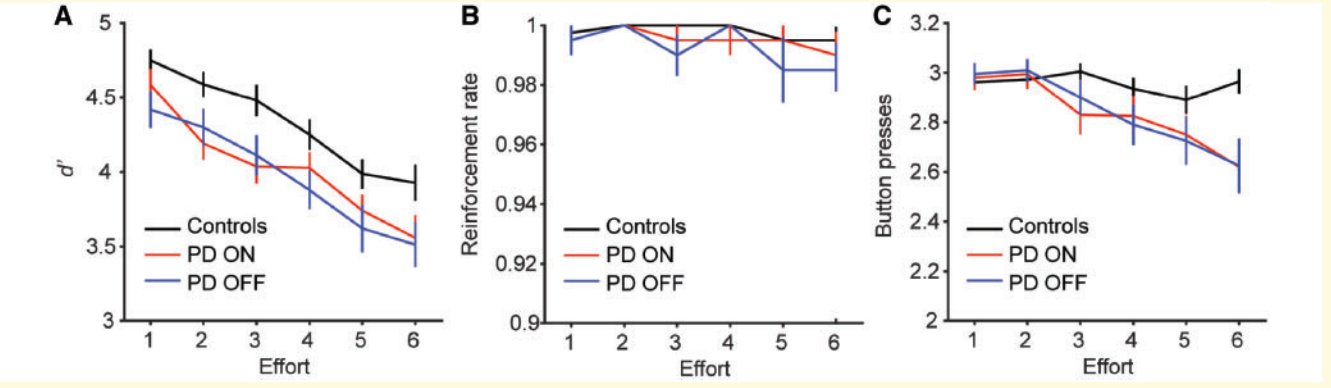

Figure 2 Data from the reinforcement phase. (**A**) Target detection sensitivity (d') decreased with increasing effort for all groups, thus confirming the cognitively demanding nature of the task. (**B**) Despite the increase in load, reinforcement rates did not differ across controls and patients, indicating the capacity of all groups to successfully perform each level of the task. (**C**) Increasing cognitive effort was not associated with an increase in physical effort requirements (button presses). PD = Parkinson's disease.

patients, both ON and OFF medication. This important result implies that the probability of being able to successfully accomplish each effort level was unlikely to have influenced subsequent decisions.

Physical load did not increase with cognitive effort

Traditionally, studies of physical effort in human and non-human animals have operationalized effort as an increasing number of lever or button-presses (Chong *et al.*, 2016). To verify that increases in cognitive effort were not accompanied by increases in physical demand, we compared the number of button presses at each effort level as a function of Group (Fig. 2C). These analyses revealed no such increases. A Group × Effort ANOVA comparing Parkinson's disease OFF and controls revealed a significant Group × Effort interaction revealing fewer button presses by Parkinson's disease OFF medication than controls at Levels 3 and 6 [Group, $F(1,38) = 3.70$, $P = 0.06$; Effort, $F(3.9,148) = 6.22$, $P < 0.001$; interaction, $F(3.9,148) = 4.75$, $P = 0.001$]. A similar interaction was found when comparing Parkinson's disease ON versus controls, with Parkinson's disease ON performing fewer presses than controls at the highest effort level [Group, $F(1,38) = 2.52$, $P = 0.12$; Effort, $F(3.4,130) = 9.71$, $P < 0.001$; interaction, $F(3.4,130) = 6.29$, $P < 0.001$]. The ANOVA comparing patients ON and OFF medication revealed only a main effect of Effort, with fewer button presses at higher levels, but no significant main effect of Drug or interaction [Effort, $F(5,95) = 11.6$, $P < 0.001$; Drug, $F(1,19) = 0.02$, $P = 0.90$; interaction, $F(5,95) = 3.6$, $P = 0.87$]. Thus, increasing cognitive effort resulted, if anything, in lower physical demands, and confirmed that our task did not confound cognitive effort with physical load.

Subjective mental demand increased with effort

Finally, to confirm that subjective mental demand increased with a greater number of streams, participants completed the mental demand subscale of the NASA Task Load Index (Hart and Staveland, 1988). Ratings for Parkinson's disease OFF and controls were compared with an ANOVA on the factors of Group and Effort. Both main effects were significant in the predicted directions, indicating that Parkinson's disease OFF medication perceived the task to be more mentally demanding than controls [Group, $F(1,38) = 10.2$, $P = 0.003$], and increasing effort was associated with greater perceived mental demand [Effort, $F(1.6,61.5) = 70.0$, $P < 0.001$; P-values for all pairwise comparisons < 0.05; interaction, $F(1.6,61.5) = 2.13$, $P = 0.14$]. The analogous ANOVA of Parkinson's disease ON versus controls, showed no difference between groups, but a persistent increase in mental demand with increasing effort [Group, $F(1,38) = 1.52$, $P = 0.23$; Effort, $F(1.7,65.1) = 67.0$, $P < 0.001$; interaction, $F(1.7,65.1) = 1.11$, $P = 0.33$]. Consistent with these data was the within-subjects ANOVA on the effect of Drug, which showed that dopamine reduced the perception of mental demand in Parkinson's disease [Drug, $F(1,19) = 5.92$, $P = 0.03$]. Effort again resulted in a progressive increase in perceived mental demand in patients [Effort, $F(1.6,30.7) = 53.9$, $P < 0.001$], without a significant interaction [$F(2.8,53.8) = 1.03$, $P = 0.39$]. In summary, all groups experienced a subjective increase in mental demand with the increasing number of RSVP streams, and the overall mental demand of the task was greater for Parkinson's disease OFF medication than either Parkinson's disease ON or controls.

Choice phase

The main question in this study was whether there were differences in the acceptance rate of cognitively effortful offers as a function of drug or disease. As for the control reinforcement data, choice data in controls did not differ across the two sessions, and were therefore collapsed.

Effect of disease

To compare the effect of disease on choice, a mixed-model ANOVA compared choices for the within-subjects factors of Effort (Levels 2–6) and Reward (2–10 points), with the between-subjects factor of Group (Parkinson's disease OFF versus Controls) (Fig. 3 and 4A). Notably, there was a significant main effect of Group, such that patients OFF medication chose the more valuable offer less frequently than controls [0.50 ± 0.03 versus 0.65 ± 0.03; $F(1,38) = 14.5$, $P < 0.001$]. In addition, there were significant main effects of Reward and Effort, which were qualified by significant two- and three-way interactions [Group × Reward, $F(2,75.5) = 3.0$, $P = 0.055$; Reward × Effort, $F(6.8,257.6) = 13.0$, $P < 0.001$; Group × Reward × Effort, $F(6.8,257.6) = 2.78$, $P = 0.009$]. Decomposing these interactions with *post hoc* Bonferroni-corrected *t*-tests indicated that the group differences between Parkinson's disease OFF and controls were greatest at the higher levels of effort and the intermediate levels of reward.

Effect of treatment

To determine the effect of drug on choice, we applied a three-way ANOVA on patients, with factors of Drug (ON, OFF), Effort (Levels 2–6) and Reward (2–10 credits) (Fig. 3 and 4B). Importantly, this revealed a significant main effect of Drug, such that patients were significantly more willing to accept the more valuable offer when ON versus OFF medication [0.65 ± 0.04 versus 0.50 ± 0.03; $F(1,19) = 14.3$, $P = 0.001$]. The remainder of this analysis indicated a main effect of Effort and Reward, and an interaction between them [Reward, $F(2.0,38.3) = 67.8$, $P < 0.001$; Effort, $F(2.1,39.0) = 60.4$, $P < 0.001$; Reward × Effort, $F(5.0,94.4) = 7.90$, $P < 0.001$]. Decomposing this interaction revealed greatest effort discounting at lower rewards, and least effort discounting at higher rewards. There were no significant interactions with Drug (all F-values < 1.57, and P-values > 0.21 for remaining interactions).

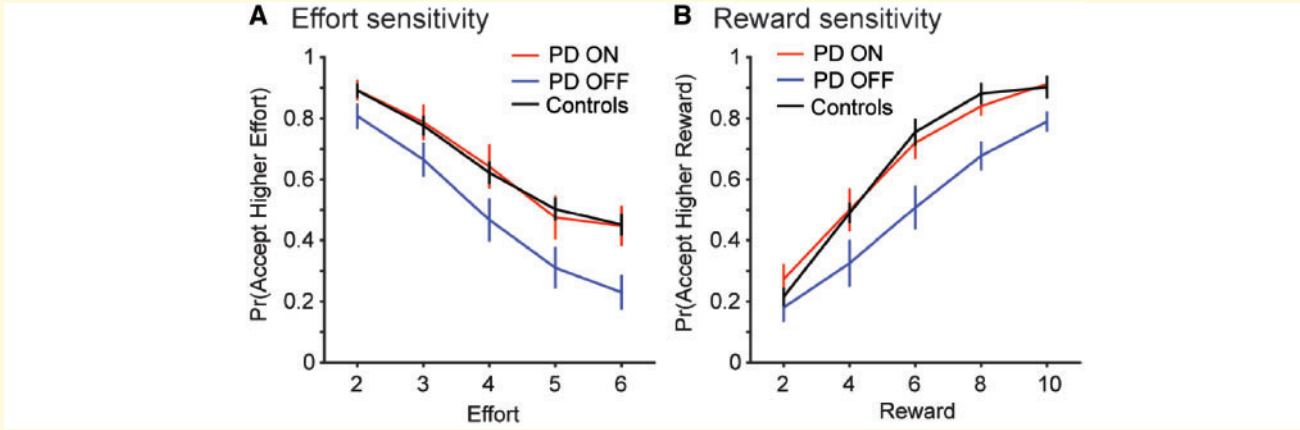

Figure 3 Acceptance rates of the high-effort/high-reward offer in controls (black), Parkinson's disease OFF medication (blue), and Parkinson's disease ON medication (red), as a function of (A) effort, and (B) reward. PD = Parkinson's disease.

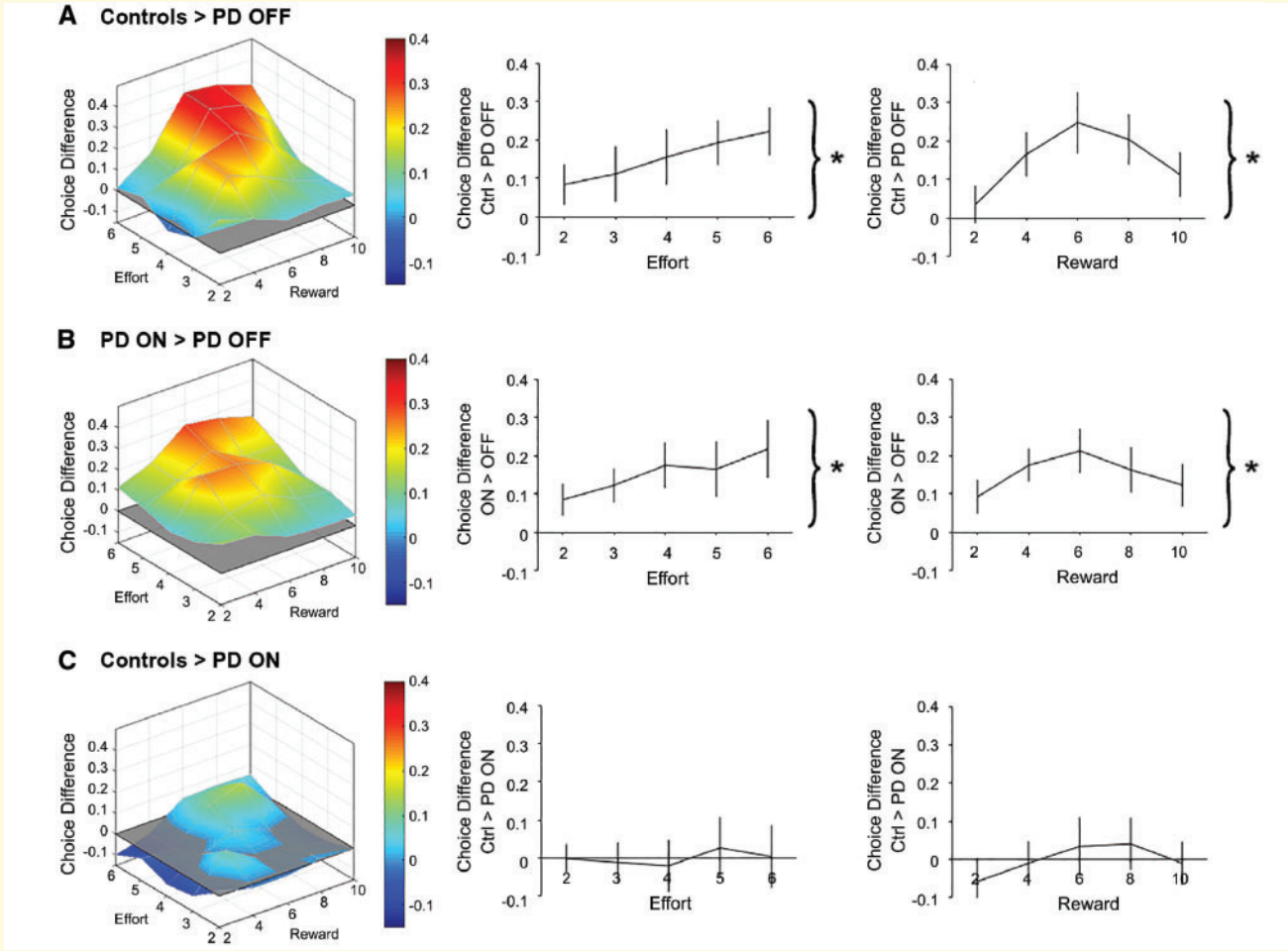

Figure 4 Difference plots of acceptance rates. Plots illustrate (**A**) the effects of disease (Controls > Parkinson's disease OFF); (**B**) the effects of treatment (Parkinson's disease ON > Parkinson's disease OFF); and (**C**) the efficacy of treatment (Controls > Parkinson's disease ON). Positive values indicate greater motivation in the reference group (i.e. controls in **A** and **C**; Parkinson's disease ON in **B**). The *leftmost* plots are 3D plots of difference in acceptance rates between the respective groups. The *middle* plots represent group differences as a function of effort, collapsed across reward, and the *rightmost* plots represent group differences as a function of reward, collapsed across effort. *Significant group differences, $P \leqslant 0.001$. PD = Parkinson's disease.

Efficacy of treatment

In keeping with the above analyses, an analogous ANOVA comparing Parkinson's disease ON versus controls revealed no statistical differences between the two groups (Figs 3 and 4C). Of note, the main effect of Group was no longer significant [0.65 ± 0.03 versus 0.65 ± 0.03; $F(1,38) = 0$; $P = 1.0$], nor were any of the Group interactions (all F-values <0.98, P-values >0.43). The main effects of Effort and Reward, and their interaction, again revealed that effort discounting decreased with increasing reward [Effort, $F(1.6,59.3) = 85.0$, $P < 0.001$; Reward, $F(2.1,81.0) = 155.5$, $P < 0.001$; Effort × Reward, $F(5.4, 204.8) = 16.9$, $P < 0.001$].

In summary, patients were less willing to invest cognitive effort compared to controls, particularly when effort requirements were high, and for intermediate reward values. Overall, however, the effect of dopamine supplementation in patients was to increase their motivation such that the behaviour of patients and controls was indistinguishable.

Computational modelling of choice

What mechanisms underlie this increase in cognitive motivation due to dopamine? Differences in motivation could potentially be manifest as changes in the gradient of an effort discounting function; its shape; and/or differences in decision stochasticity (Beeler *et al.*, 2010; Chong *et al.*, 2017, 2018*a*). To address this issue, we applied computational models of choice behaviour to estimate the subjective value of each offer to individual participants. We fitted participants' responses to three functions—linear, parabolic and hyperbolic functions—which are typically used to capture effort discounting (Prévost *et al.*, 2010; Hartmann *et al.*, 2013; Skvortsova *et al.*, 2014; Klein-Flügge *et al.*, 2015; Lockwood *et al.*, 2017). The shapes of these functions reflect how the perception of increasing effort affects choice behaviour. Linear models predict constant discounting as effort increases; hyperbolic (convex) models predict that changes at lower levels of effort will have greater impact than changes at higher levels; and parabolic (concave) models would predict the opposite.

Specifically, our functions were:

$$Linear: SV(t) = R(t) - k \cdot E(t) \quad (1)$$

$$Parabolic: SV(t) = R(t) - k \cdot E(t)^2 \quad (2)$$

$$Hyperbolic: SV(t) = R(t) \cdot \frac{1}{1 + k \cdot E(t)} \quad (3)$$

where $SV(t)$ represents the subjective value of the offer on trial t; R is the reward in credits (2, 4, 6, 8, 10); E is the effort involved (1 to 6 streams); and k is a subject-specific effort discounting parameter, which describes the gradient of each individual's discounting function. Thus, the higher the k-value, the less motivated an individual.

For each group, we fitted these three functions to choices in each of the two sessions (i.e. $3^2 = 9$ models each for patients and controls). The subjective value of each offer for each subject was referenced to the subjective value of the baseline offer. Models were fit using a *softmax* function and maximum likelihood estimation, with the *softmax* function being defined as:

$$Pr(i) = \frac{e^{\beta \cdot SV_i}}{e^{\beta \cdot SV_b} + e^{\beta \cdot SV_i}} \quad (4)$$

where $\Pr(i)$ represents the probability of choosing option i that has a subjective value of SV_i relative to the baseline option b with subjective value of SV_b; and β is the inverse temperature of the *softmax* function. β defines the stochasticity of decisions, with a value of zero corresponding to maximum stochasticity, and increasing β implying a more invariant, maximising, strategy in which the higher value offer is chosen more frequently. The effort discounting parameter (k) and the inverse temperature (β) were modelled separately for each session. We compared model fits for each group with an Akaike Information Criterion (AIC) and a Bayesian Information Criterion (BIC).

The results of this analysis revealed that a linear effort discounting function provided the best fit for the choices of both controls and patients in both testing sessions (Equation 1 above). Specifically, the model in controls that comprised linear effort discounting functions for both sessions won by 33 AIC (or BIC) units. Similarly, the model in patients that was composed of linear discounting functions for both the ON and OFF sessions won by 24 AIC (or BIC) units. To quantify the likelihood that this combination of models best accounted for choice behaviour across the entire group of patients and controls, we computed the Akaike weights for each of the $9^2 = 81$ models across the entire model space. Akaike weights represent the relative likelihood of a model relative to other models in the space, and are given by:

$$w_i(AIC) = \frac{e^{-0.5 \cdot \Delta_i(AIC)}}{\sum_{m=1}^{M} e^{-0.5 \cdot \Delta_m(AIC)}} \quad (5)$$

where $w_i(AIC)$ = the Akaike weight of model i; $\Delta_i(AIC)$ = the difference in AIC between model i and the best fitting model; and M = the number of models in the space. This analysis revealed that the relative likelihood that this combination of model fits best explained motivation across the group was 1.0 (Fig. 5A). The analogous computation for BIC values was undertaken with Schwarz weights, which yielded the equivalent result (Fig. 5B). In summary, dopamine did not appear to have a significant effect on altering the fundamental (linear) pattern of cognitive effort discounting across groups or within patients.

Next, we compared the model parameters (k and β) for the winning model. The analysis on k-values reiterated the result from the main analysis on acceptance rates (Fig. 5C). Specifically, k-values were higher for Parkinson's disease OFF compared to controls [Parkinson's disease OFF, 1.84 ± 0.17 versus Controls, 1.26 ± 0.12, $t(38) = 2.79$, $P = 0.008$]. Being ON dopamine significantly decreased

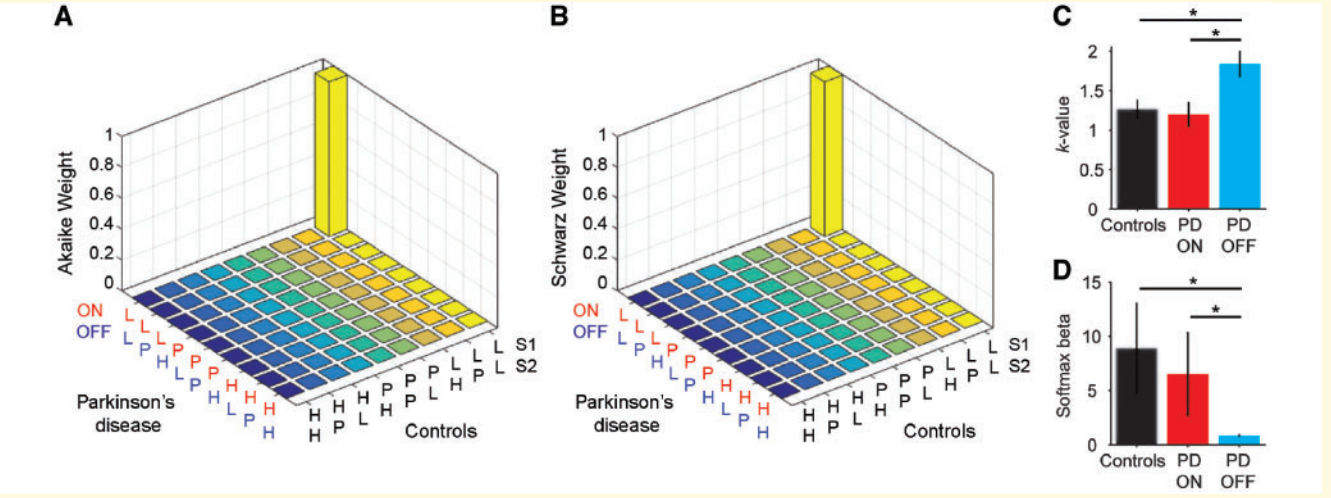

Figure 5 Results of the computational models. Our model space included all possible combinations of linear (L), parabolic (P), and hyperbolic (H) effort discounting functions in each of the two sessions performed by patients and controls. Results of the model comparison revealed that linear functions best fit choices from participants in both groups in both sessions (ON and OFF for patients; Session 1 and Session 2 for controls). This was confirmed by the high (**A**) Akaike weights, and (**B**) Schwarz weights, for those models. (**C**) *k*-values were significantly higher for Parkinson's disease OFF medication, indicating lower motivation, compared to controls and Parkinson's disease ON. (**D**) Inverse temperature parameters (β) were significantly lower in Parkinson's disease OFF medication, indicating greater choice stochasticity, relative to controls and Parkinson's disease ON. PD = Parkinson's disease.

the *k*-values in patients relative to the OFF state [Parkinson's disease OFF, 1.84 ± 0.17, versus Parkinson's disease ON, 1.20 ± 0.16, $t(38) = 3.05$, $P = 0.007$], and eliminated the difference to controls [$t(38) = -0.32$, $P = 0.75$]. This significant effect of drug in improving cognitive motivation in Parkinson's disease did not differ as a function of whether patients scored in the 'apathetic' range on their total DAS score (Supplementary material).

Interestingly, we also found group differences for the inverse temperature (β) values for Parkinson's disease OFF medication relative to controls and Parkinson's disease ON (Fig. 5D). Because of non-normalities in the data, we applied non-parametric independent samples Mann-Whitney U-tests to compare parameter estimates for controls and patients, and a paired Wilcoxon signed-ranks test to compare those for Parkinson's disease ON and OFF medication. These analyses revealed that controls had a significantly greater β than patients OFF medication, indicating greater choice stochasticity in the latter group (Controls, 7.72 ± 3.81, versus Parkinson's disease OFF, 0.84 ± 0.13, $U = 89$, $Z = 2.99$, $P = 0.003$). We also found that being ON medication increased the β-values relative to being OFF (Parkinson's disease ON 7.18 ± 4.46, versus Parkinson's disease OFF, 0.84 ± 0.13, $W = 51$, $Z = 2.02$, $P = 0.04$), and restored them to equivalent levels to controls ($U = 152$, $Z = 1.28$, $P = 0.20$).

Overall, these results showed that dopamine increased cognitive motivation, not by altering the fundamental shape of the discounting function in Parkinson's disease, but merely by reducing its gradient. This greater motivation was also associated with altered decision stochasticity, with greater variability when Parkinson's disease patients were OFF medication relative to healthy controls, and when they were ON medication.

Trait measures of cognitive apathy predict cognitive effort discounting

How specific was our measure of cognitive effort discounting to trait measures of cognitive apathy? To address this question, we pooled data from all participants by taking subject-specific *k*-values for controls and patients OFF medication (to avoid confounding the effect of treatment on responses), and performed a multiple regression of these values against individual scores on each subscale of the DAS (Fig. 6). We note that one patient had a *k*-value that was >3.8 standard deviations (SDs) above the group mean—to minimize the effect of such outliers, we applied a robust multiple regression-based analysis with Huber's method of correction, and included group as a dummy variable ('0' for controls and '1' for patients).

Importantly, this revealed that *k*-values were uniquely and specifically predicted by the only subscale of the DAS that measures cognitive apathy (namely, the Executive subscale, $\beta = 0.07$, $P = 0.04$). In contrast, the regression coefficients for the remaining two DAS subscales were not significant (Emotional, $\beta = 0.02$, $P = 0.49$; Behavioural, $\beta = 0.004$, $P = 0.87$). No significant correlations were found between patients' *k*-values and disease parameters (namely, disease duration, UPDRS scores, and levodopa equivalent doses).

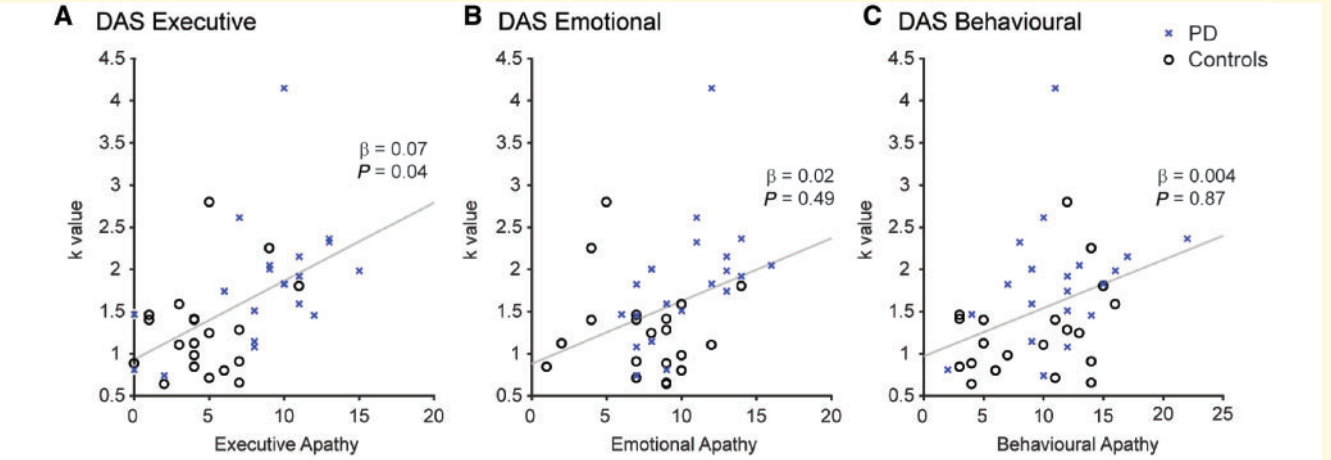

Figure 6 Scatter plot of *k*-values against responses on individual subscales of the DAS. Higher *k*-values indicate less motivation. Higher DAS scores indicate greater apathy. A robust regression showed a significant relationship between *k*-values and the (**A**) Executive subscale, but not the (**B**) Emotional or (**C**) Behavioural subscales. Cross symbols indicate patients, circles indicate control subjects. PD = Parkinson's disease.

Reinforcement rates and task performance did not affect choice

Finally, we confirmed that the aversion to investing higher levels of effort was not due to a lower likelihood of succeeding at those levels (i.e. probability discounting). This was unlikely, given that reinforcement rates did not differ across groups (Fig. 2B). Nevertheless, to address this issue, we performed a logistic regression on choices for each patient separately, including the factors of Drug, Reward, Effort, and Reinforcement rate (Fig. 7A). Parameter estimates (β-values) for each patient were normalized to *t*-statistics as [β/SE(β)] to compensate for the possibility of low levels of variance leading to poor beta estimates for any variable (note, however, that the pattern and direction of results were unchanged for raw beta values). To determine which of the factors had a significant (non-zero) influence on choice behaviour, we compared the *t*-statistics for each factor against zero with non-parametric Wilcoxon signed-ranks test (due to the non-normality of the data).

Importantly, the *t*-statistics for reinforcement rate did not significantly differ from zero, indicating that it did not influence patients' choices ($t_{rf} = 0.63$, $P = 0.40$). The remainder of the logistic regression reiterated the main result above, such that Drug significantly increased the likelihood of accepting the offer ($t_{drug} = 2.13$, $P = 0.006$), and Reward and Effort had significant positive and negative effects on choice, respectively ($t_{rew} = 5.35$, $P = 0.0001$; $t_{eff} = -4.74$, $P = 0.0001$). The analogous logistic regression on controls, with the factors of Session, Reward, Effort and Reinforcement rate, revealed a similar pattern of results, by showing that Reward and Effort had significant positive and negative influences on choice (respectively), but that neither Session nor Reinforcement Rate affected participants' decisions ($t_{sess} = 0.34$, $P = 0.53$; $t_{rf} = 0.18$, $P = 0.47$; $t_{rew} = 4.59$, $P = 0.0001$; $t_{eff} = -4.26$, $P = 0.0001$).

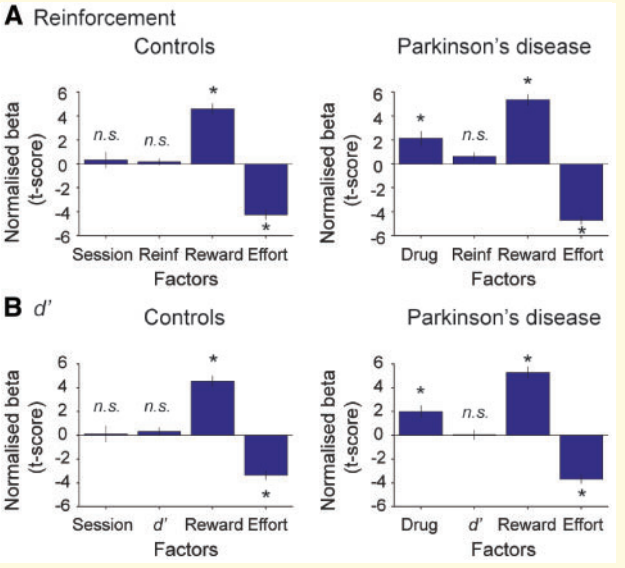

Figure 7 Logistic regression of choice data in Controls, and Parkinson's disease. Importantly, performance in the reinforcement phase [either as (**A**) reinforcement rates or (**B**) *d'*] did not significantly influence choice (i.e. parameter estimates were not significantly different from zero). The remaining results reiterate the previous analyses on acceptance rates, indicating a significant positive effect of Reward and negative effect of Effort on choice. Control behaviour was no different between sessions. In patients, being on Drug had a significant positive impact on choice. *$P < 0.05$.

Could patients' lower willingness to invest effort at the higher levels be due to poorer ability to perform the more effortful levels? This is again unlikely, given that medication in patients resulted in a change in acceptance rates, but not in *d'*. Nevertheless, we formally tested this possibility

by performing a separate logistic regression, on factors of Drug, Reward, Effort and d' (Fig. 7B). This regression revealed the identical pattern of results to the initial analysis, with no significant effect of d' on choice ($t_{d'} = 0.04$, $P = 0.94$; $t_{drug} = -1.98$, $P = 0.005$; $t_{rew} = 5.30$, $P = 0.0001$; $t_{eff} = -3.68$, $P = 0.0001$). The analogous logistic regression on controls (on Session, Reward, Effort, d') revealed the same pattern of results as for Reinforcement rates ($t_{sess} = 0.10$, $P = 0.88$; $t_{d'} = 0.33$, $P = 0.19$; $t_{rew} = 4.56$, $P = 0.0001$; $t_{eff} = -3.35$, $P = 0.0001$). Finally, the corresponding analyses on hits and false alarm rates revealed no significant effect of either of these factors on choice (Supplementary material).

Overall, therefore, these analyses indicate that dopamine was able to increase motivation in the ON relative to OFF medication states independent of any effects on task performance or likelihood of success.

Discussion

This study is the first to demonstrate a critical role for dopamine in cognitive motivation. Our data revealed four key findings. First, patients with Parkinson's disease OFF medication were less willing to invest cognitive effort for reward than their healthy age-matched counterparts. Second, this motivational impairment was ameliorated by dopamine replacement. Third, dopamine had independent effects on choice stochasticity, such that decisions by patients OFF medication were more variable than controls and when they were ON dopamine. Finally, cognitive motivation was uniquely related to the only subscale of the DAS that specifically indexes cognitive apathy. Importantly, these results could not be accounted for by probability discounting, varying task performance, temporal discounting, or increasing physical demands. By demonstrating that the role of dopamine in overcoming effort generalizes to the cognitive domain, these data provide important evidence in favour of prominent frameworks that posit a central, domain-general role for dopamine in motivated behaviour.

Several studies have demonstrated that dopamine therapy, in particular with dopamine agonists, ameliorates parkinsonian apathy as assessed on standard rating scales (Czernecki *et al.*, 2002; Thobois *et al.*, 2013; Chong and Husain, 2016). However, investigations of dopamine in human effort-based decision-making have focused exclusively on physical effort (Wardle *et al.*, 2011; Treadway *et al.*, 2012; Chong *et al.*, 2015, 2018*b*; Le Bouc *et al.*, 2016; Le Heron *et al.*, 2018). Although it is clear that dopamine facilitates physical effort-based decisions independent from its activational effects on motor facilitation, energization and invigoration (Niv *et al.*, 2007; Salamone and Correa, 2012), an important unanswered question is whether this motivational effect of dopamine generalizes to other effort costs (Kurzban *et al.*, 2013; Cools, 2015; Verguts *et al.*, 2015; Shenhav *et al.*, 2017; Chong, 2018). Recent theoretical frameworks have proposed that dopamine might play a broader role in cost-benefit valuation, by providing a value estimate of 'working', or how worthwhile it is to expend internal resources (Hamid *et al.*, 2016). By such accounts, these resources need not be physical (i.e. motor), but should extend to any resources that are limited in capacity (e.g. cognitive), and that would incur a significant cost should they be engaged (such as a temporal or opportunity cost) (Berke, 2018). Indirect evidence for this proposal arises from patients with schizophrenia, whose negative symptoms have been associated with an increased subjective cost of cognitive effort (Culbreth *et al.*, 2017). Our main finding—that cognitive apathy in Parkinson's disease is ameliorated by dopamine—provides direct and confirmatory data for such frameworks.

How might such a domain-general mechanism be instantiated? The striatum receives substantial input from the medial prefrontal cortex, as well as from limbic structures such as the amygdala (Fudge *et al.*, 2002; Haber and Knutson, 2010; Cho *et al.*, 2013; Chau *et al.*, 2018). Recent neuroimaging data implicate these regions as key nodes in a network that represents effort-related costs. Both the striatum and medial prefrontal cortex encode effort costs independent of the specific domain of effort (Schmidt *et al.*, 2012; Chong *et al.*, 2017). In contrast, the amygdala has been shown across species to uniquely encode cognitive effort costs (Hosking *et al.*, 2014; Chong *et al.*, 2017). Together, this cortico-amygdala-striatal circuit offers a plausible mechanism through which dopamine can exert its effects on cognitive effort valuation (*cf*, Verguts *et al.*, 2015), through both domain-general pathways (via the striatum and medial prefrontal cortex) and domain-specific routes (via the amygdala).

It is important to note that the greater motivation in patients ON versus OFF medication occurred despite no differences in their capacity to perform the task itself. The reinforcement data indicate that medication had no effect on target detection sensitivity (d'), reinforcement rates, or the physical demands of the task. In addition, the temporal parameters of all effort levels in all sessions were held constant. Furthermore, the logistic regressions definitively confirmed that behavioural performance during the reinforcement phase could not account for subsequent choice behaviour. This is similar to previous studies in healthy participants, which have reported cognitive effort discounting even after carefully controlling for reward likelihood (Kool *et al.*, 2010; McGuire and Botvinick, 2010; Westbrook *et al.*, 2013; Chong *et al.*, 2017). Together, therefore, the lower motivation in patients OFF versus ON medication can only be attributed to a greater aversion to the investment of effort costs, independent of other factors that might confound effort-based decisions.

Several paradigms have recently been used to manipulate cognitive effort in humans (Westbrook *et al.*, 2013; Kool and Botvinick, 2014; Vassena *et al.*, 2014; Apps *et al.*, 2015). Although the precise pattern of cognitive effort discounting is likely to be task-specific [e.g. previous work using a different cognitive manipulation resulted in

hyperbolic, rather than linear, discounting (Chong *et al.*, 2017)], we would nevertheless expect the effect of dopamine to generalize to other capacity-limited cognitive domains. It is interesting to note, therefore, that the only other study on dopamine in cognitive effort-based decision-making found no effect of dopamine antagonism on the willingness of rodents to invest cognitive effort (Hosking *et al.*, 2015). One of the more significant task differences that likely underlies this discrepancy is the effort-reward space that was sampled in each study. The rodent task offered a relatively narrow range of rewards (either one or two pellets) for performing one of two levels of effort [detecting a brief (0.2 s) or more sustained (1 s) flash of light]. As shown in our data, choice behaviour varies considerably across individuals, and the main difference between controls and Parkinson's disease OFF medication was mainly found at high levels of effort and intermediate levels of reward. It is possible that the wider and more granular space in our study was more sensitive to the effects of drug and disease. Ideally, future studies on non-human animals should aim to directly confirm our results in a task in which reward and cognitive effort are parametrically varied over multiple levels.

In addition, our models revealed that dopamine not only increased the subjective value of discounted rewards, but also reduced the stochasticity of cognitive effort choices. The inverse temperature (β) of the *softmax* function quantifies the consistency with which individuals choose the higher value option, and was significantly lower in patients OFF medication, relative to controls and Parkinson's disease ON drug. β is often described as regulating the balance between exploration and exploitation, and previous studies indicate that animals may benefit from intentionally imposing variability on their choices when there is greater uncertainty about the environment (Sutton and Barto, 1998; Cohen *et al.*, 2007). In the context of our Parkinson's disease sample, one possible interpretation is that striatal dysfunction led to noisier representations of effort costs, and a subsequent shift away from a value-maximizing strategy towards more exploratory choice behaviour (Beeler *et al.*, 2010). Broadly, this proposal that dopamine may modulate the expression of motivated behaviour by increasing the consistency, or gain, with which effort and reward are processed is in keeping with incentive salience theories of dopamine function (Berridge, 2007).

Cognitive effort discounting on our task was strongly and specifically correlated with subjective trait measures of cognitive motivation, over and above measures of behavioural and emotional motivation. Previous studies in healthy individuals have shown a relationship between cognitive effort and responses on scales of cognitive engagement [e.g. the Need for Cognition Scale (Cacioppo *et al.*, 1984; Westbrook *et al.*, 2013)]. Our results not only replicate these findings using a different task and a different scale, but extend them to show that this correlation is specific to trait measures of cognitive motivation (the executive subscale of the DAS), and not to other domains of apathy (behavioural and emotional) on the same scale. This indicates that our measure of cognitive effort discounting was able to capture the cognitive element of motivation that is distinguished by current frameworks of apathy, and provides support for the link between objective laboratory measures of motivation (the *k*-parameter), and subjective reports of day-to-day motivation.

Although the recent focus on apathy has centred on dopaminergic pathways, the complex mechanisms underlying human motivation are likely to be driven by multiple neurotransmitter systems. In the case of cognitive apathy, cholinergic pathways may be particularly relevant, as disruption of these networks in Parkinson's disease have been associated with both cognitive dysfunction (Svenningsson *et al.*, 2012), and apathy in general (Bohnen *et al.*, 2007). Interestingly, Parkinsonian apathy as assessed on standard rating scales also appears to be responsive to treatment with cholinesterase inhibitors (Devos *et al.*, 2013). The precise relationship between acetylcholine and cognitive apathy remains to be elucidated, and understanding the complex interplay between the cholinergic and dopaminergic systems will be crucial in refining current theoretical frameworks of apathy.

Cognitive effort has recently been a focus of intense interest, but its neurobiology has been poorly characterized. Here, we present the first evidence that dopamine causally modulates cognitive motivation in humans. This has broad clinical and theoretical implications. From a clinical perspective, these data emphasize the importance of optimizing dopaminergic therapy, not only to improve the motor symptoms and physical motivation in patients with Parkinson's disease, but also to improve their willingness to engage in cognitively demanding behaviour, which might be central for rehabilitative goals. More broadly, these results provide important empirical support for recent theories that have assumed a domain-general role of dopamine in value-based decision-making, and therefore provide a critical link between dopamine and multidimensional theories of motivational disorders.

Acknowledgements

The authors wish to express their gratitude to all participants, and to Parkinson's Victoria for their assistance with patient recruitment.

Funding

T.C. is supported by the Australian Research Council (DP 180102383, DE 180100389), the Judith Jane Mason and Harold Stannett Williams Memorial Foundation, the Brain Foundation, the Rebecca L Cooper Medical Research Foundation, and the Society for Mental Health Research.

D.T. is supported by the Bethlehem Griffiths Foundation. M.A.B. is supported by the Australian Research Council and National Health and Medical Research Council of Australia.

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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