Dopamine and motivational state drive dynamics of human decision making

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ABSTRACT

The mesolimbic dopaminergic system exerts a crucial influence on normal motivated behaviour, but the mechanism of this action in dynamic situations where decisions evolve over time remains unclear. In such circumstances, current (foreground) reward accrual rate needs to be compared continuously with potential rewards that could be obtained elsewhere (background reward rate) in order to determine the opportunity cost of staying or leaving. We hypothesised that dopamine levels specifically modulate the influence of background – but not foreground – reward information in a decision-making task that requires dynamic comparison of these variables for optimal behaviour, and that this effect would be disrupted in individuals with loss of motivation – apathy. We developed a human foraging task based on a normative theory of animal behaviour (marginal value theorem), in which participants decide when to leave locations in which rewards decreased over time in order to pursue greater returns in their environment. People's decisions to move from current locations conformed closely to foraging principles. Pharmacological manipulation of dopamine D2 receptor activity in healthy individuals using the agonist cabergoline significantly modulated background, but not foreground, reward sensitivity. In a separate study, this same effect was observed in patients with Parkinson's disease, dependent on presence of apathy. Using an ecologically derived framework we demonstrate a specific mechanism by which dopamine modulates dynamic human decision-making, and how impairment of this mechanism can contribute to pathological loss of motivation.

KEY WORDS

Dopamine; Apathy; Decision making; Reward; Foraging; Opportunity cost; Parkinson's Disease

INTRODUCTION

The mesolimbic dopaminergic system plays a crucial role in motivating behaviour towards goals and has been closely linked to neural circuits which convey information about rewards (1–6). Several experiments across species have demonstrated a crucial role for dopamine in overcoming costs to obtain rewards (2,3,7,8) and for learning about reward outcomes to update future behaviour (9,10). Tasks probing dopamine function typically require an agent to make *binary decisions* between presented options, based on learning the contingent relationship between stimuli and rewards, or an integration of cost and reward information (8,9,11). However, animal models increasingly highlight that dopamine signals change during on-going behaviours and carry information that is not exclusively tied to reward predicting cues (1,12,13).

Moreover, in many real-life environments choices are not between binary options, but instead evolve over time, involving decisions of whether to stay at the current location or switch to an alternative one to maximize reward collection (14,15). Such dynamic decision-making requires continuous comparison between current (foreground) reward rate relative to the alternative (background) reward rate available in an agent's environment (16–18). However, despite the clear ecological significance of such foreground vs background decision making for normal motivated behaviour, the role of dopamine in modulating these processes – and particularly when to switch from a current activity to pursue greater rewards in the background environment – remains unclear.

Based on work examining the relationship between speed of movement (vigour) and dopamine in animal models, it has been proposed that tonic (slower-changing) dopamine signals encode information about environmental richness, and therefore background reward rate (19). This theory is supported by recent voltammetry experiments linking slow (minute-by-minute) changes in dopamine levels to an experimental rodent's reward environment (1), and evidence of changes in motor vigour as dopamine state varies in humans (3,8,20,21). However this link has been questioned (22), and it remains unknown whether the proposed link between tonic dopamine and vigour of movements applies to more abstract – but ecologically crucial – decisions about when to switch location based on foreground and background reward rates. Nor is it clear whether these principles would apply to how humans make such decisions.

Foraging models of behaviour, described originally within the behavioural ecology literature, provide an ideal theoretical framework within which to investigate the relationship between dopamine and dynamic human decision making. An accurate representation of background reward rate is a crucial component of the ecological problems described by such foraging models, including the Marginal Value Theorem (MVT) (23,24). MVT characterises and precisely quantifies how a fundamental decision – when to leave a location in which rewards are depleting over time, to search for a better location ("patch") in the environment – should be made (**Supplemental Figure 1).** The optimal solution to this patch leaving problem is achieved by comparing the foreground reward rate – the value of *what an agent is doing right now* – with the background reward rate – the average value of *what else it could be doing* (the opportunity cost). As soon as the instantaneous foreground reward rate in a patch drops below the average background reward rate, an optimal forager should leave and travel to the next patch (14,23,24). The behaviour of a wide range of species has been shown to follow MVT predictions (25,26), However, despite the clear importance of such decisions in the evolution of the human brain (14,15), little is known about the mechanisms underlying human patch leaving behaviour, and particularly the role of dopamine in putatively signalling background average reward rate.

From a clinical perspective, impairment of mechanisms underlying foreground/background decision making may underlie pathological apathy, a disabling disorder of motivated, goal directed behaviour (27). Apathy is a common feature of many psychiatric and neurological disorders, and identification of mechanisms underlying the syndrome remains a crucial challenge for development of effective treatments (28). In Parkinson's disease (PD) it has been linked to alterations in mesolimbic dopaminergic systems (27,29,30), reduced physiological responses to rewards (31,32), and reduced willingness to exert effort for reward (3,8). Furthermore, apathy can be successfully treated in some patients with dopamine agonists, which selectively stimulate D2 and D3 receptors (33,34). A foreground/background decision making framework can potentially unite the above observations. If tonic dopamine levels signal background reward rate – a crucial contextual cue for when to switch behaviour – apathetic patients, in whom these dopamine levels are reduced, may be less inclined to switch from their current (foreground) activity, even if this activity involves doing very little. However, the relationship between dopamine, apathy and different components of reward (foreground and background) has never been examined.

We hypothesised that tonic dopamine levels would selectively modulate the influence of background reward rate within an ecologically grounded decision-making task requiring dynamic comparisons between foreground and background reward rates. We further hypothesised that this effect would be contingent on motivational state, and that apathetic individuals would show aberrant background reward sensitivity, linked to dopamine levels. We developed a novel patch leaving paradigm in which the behavioural effect of changing foreground and background reward rates could be dissociated. In a series of studies using this paradigm we investigated the specific role of dopamine in modulating decisions to move on. D2 receptor stimulation using the dopamine agonist cabergoline was tested in healthy participants as they made patch leaving decisions. We then assessed apathetic and non-apathetic patients with PD, ON and OFF their normal dopaminergic medications, to investigate how these effects were influenced by pathological loss of motivation.

Across the three studies we demonstrate that healthy human participants make patch leaving decisions in accordance with MVT principles, adjusting for changes in foreground and background reward rates in close to optimal manner. Manipulating dopamine levels alters this sensitivity to *background*, but not foreground, reward rates, consistent with theories that dopamine signals information about average reward rates. Finally, in PD the presence of apathy modulates this dopaminergic effect, elucidating an underlying cognitive mechanism for this debilitating syndrome.

RESULTS

All participants were administered a computer based patch-leaving task in which they had to decide when to move on from a current patch. The task design specifically manipulated the background and foreground reward rates, in line with the predicted effects according to MVT (23,24).

The task was framed as a farming game in which participants had to collect as much milk (reward) as possible – this would be sold at a market at the end of the game and their financial remuneration would therefore be according to the milk accrued. Participants spent a fixed time (10 minutes) in each of two farms, collecting milk from fields of cows and making

decisions of whether to move on (leave the field for the next one) (**Figure 1**). Moving on to the next field incurred a time cost of 6 seconds, during which no milk could be collected.

To manipulate the foreground reward rate, there were three field-types, which returned milk at high, medium and low rates, which exponentially decayed over time in the field. The field-type was indicated by the rate at which the bucket on the screen filled. The distribution of these field-types within a "farm" determined the background reward rate.

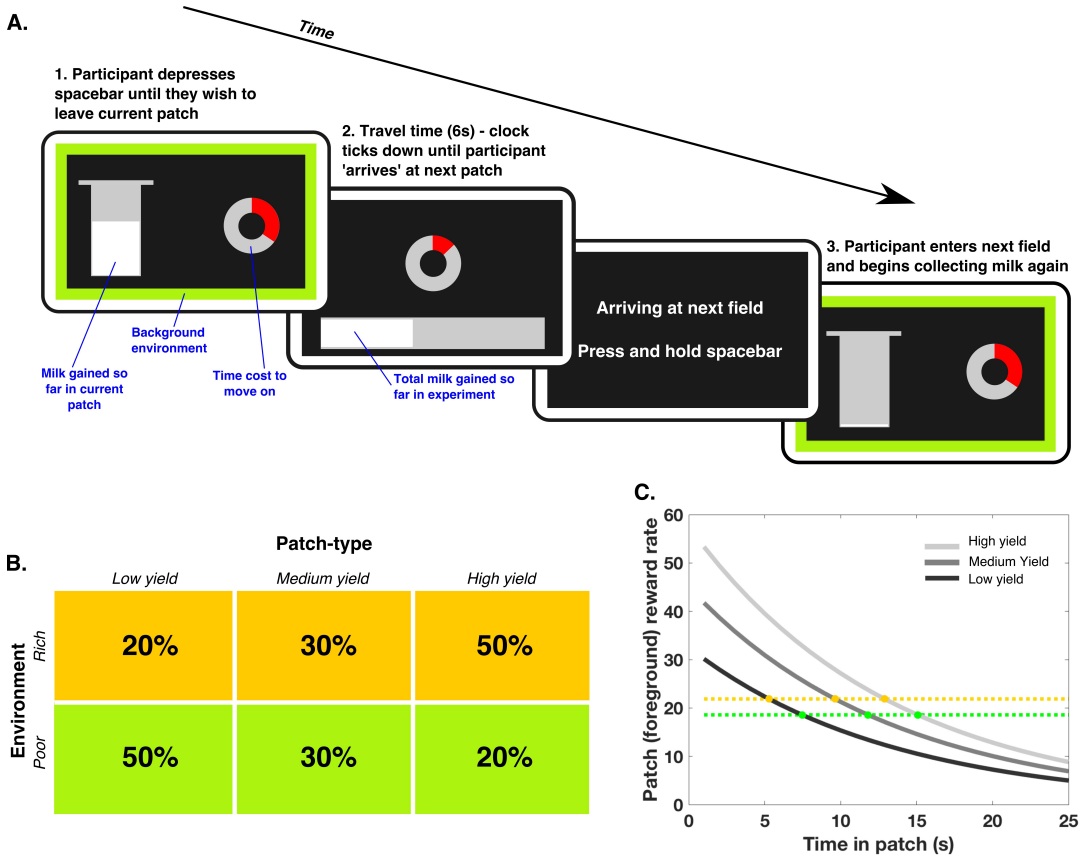

Figure 1. Patch leaving paradigm

(**A**) Participants had to decide how long to remain in their current patch (field), in which reward (milk) was returned at an exponentially decreasing rate (displayed on the screen by continuous filling (white bar) of the silver bucket), before moving on to the next patch, which incurred a fixed cost of 6 seconds during which they could collect no reward. Their goal was to maximise milk return across the whole experiment. The instantaneous rate of bucket filling indicated the **foreground reward rate**, whilst the coloured frame indicated the distribution of different patch types, and thus the **background reward rate**. Participants were aware they had approximately 10 minutes in each environment, but were not shown any cues to indicate how much total time had elapsed. Following a leave decision, a clock ticking down the 6 second travel time was presented. (**B**) Three foreground patch-types were used, differing in the scale of filling of the milk bucket (low, medium and

high yield), which determined the foreground reward rate. Two different background environments (farms) were used, with the background reward rate determined by the relative proportions of these patch-types. The gold farm contained a higher proportion of high yield fields, and a lower proportion of low yield ones, meaning it had a higher background reward rate than the green farm, which had a higher proportion of low yield fields. (**C**) According to MVT participants should leave each patch when the instantaneous reward rate in that patch (grey lines) drops to the background environmental average (gold and green dotted lines). Therefore, people should leave sooner from all patches in rich (gold dotted line) compared to poor (green dotted line) environments, but later in high yield compared to low yield patches. Crucially, these two effects are independent from each other.

On the "rich" farm (signalled by a gold border on the screen) 50% of encountered fields were high yield, 30% were medium yield and 20% were low yield. On the "poor" farm (signalled by a green border) 50% of encountered fields were low yield, 30% medium and just 20% high yield. Thus, the background reward rate was lower on the green farm than the gold farm. Participants were aware that an unlimited number of fields were available to them, but for only a fixed amount of time. The influence of foreground and background reward rates, and where relevant dopamine and apathy, on patch leaving time was analysed using a linear mixed effects model (LME) – see **Methods** for further details.

Healthy human foragers are guided by MVT principles

Within MVT the foreground and background reward rates should have independent effects on how long an individual remains in a patch. Participants should leave low yield patches sooner than high yield patches, and patches in rich environments sooner than patches in poor environments. In line with these hypotheses, we found a main effect of foreground reward, a main effect of background reward, but no interaction on participants' (N = 39) decisions about when to leave their current patch (Foreground: $F(1,74.6) = 528$, $p < 0.0001$; Background: $F(1,37.5) = 40$, $p < 0.0001$; Foreground × Background: $F(1,1929) = 1.6$, $p = 0.2$; **Supplementary Table 1A**). Furthermore, participants' behaviour conformed to predicted directionality of these effects, with higher patch yield, and poor compared to rich background environment, both leading to later patch leaving times (**Figure 2A & 2B**).

Are healthy people optimal foragers?

Although participants showed effects in the directions predicted by MVT, we wanted to know whether the *magnitude* of these effects conformed to foraging theories, which stipulate exactly the optimal time to leave each patch (**Supplemental Figure 1**). All participants showed a significant bias to remain longer across all patch types (across both environments)

than optimal, on average leaving 8.0s later than MVT predictions ($t_{38} = 8.4$, $p < 0.001$, **Supplemental Figure 2A & B**). However, it has been noted that non-human primates also show a bias to stay, but are close to optimal once controlling for this bias, for example by analysing the *relative changes* across conditions (35). Therefore for each participant we subtracted their own mean leaving time from each of their patch leaving decisions, and calculated the magnitude of the *background* (poor − rich) and *foreground* (high − low yield) reward rate effects (**Figure 2B & 2D**).

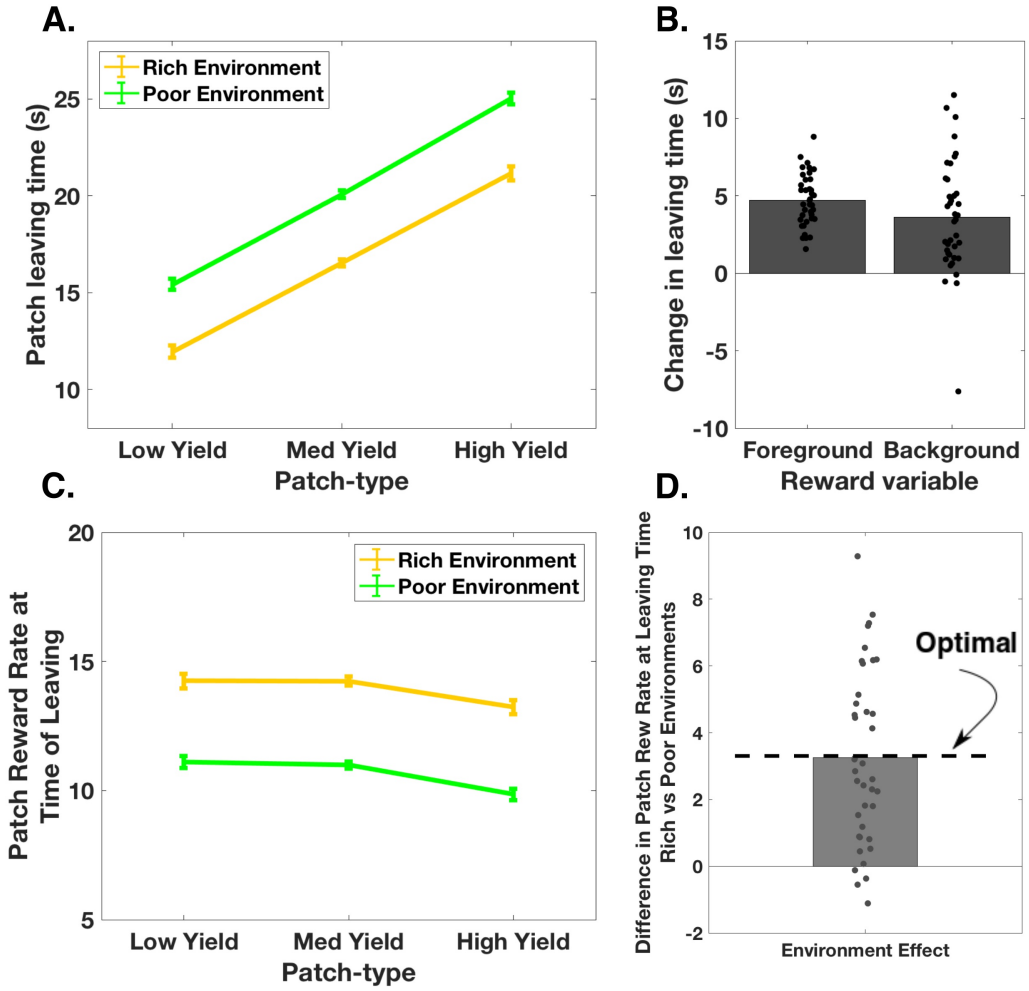

Figure 2. Healthy human foragers are guided by MVT principles.

(**A**) Participants (N = 39) left patches later when the background environment was poor, compared to rich ($p < 0.00001$), and when patches had higher, compared to lower yields ($p < 0.00001$), with no interaction between patch-type and background environment ($p = 0.2$). (**B**) These effects of changing reward parameters were in the predicted direction, with participants leaving on average 4.7s later as patch-type varied, and 3.6s later in poor

compared to rich environments. There was more variation between individuals in the effects of changing background, compared to foreground, reward rates. (**C**) The foreground (patch) reward rate at which participants chose to leave each patch varied as a function of background environmental richness (rich vs poor). (**D**) The magnitude of this background environment effect was close to optimal (as predicted by the marginal value theorem). Foreground reward rate at leaving did vary across patch-type (indicating a degree of suboptimal behaviour) (**C**), driven by participants leaving high yield patches at a lower reward rate compared to medium and low yield patches, which did not differ significantly. Error bars are ± SEM.

MVT makes two core predictions about behaviour as foreground and background reward rates change, which can be used to assess optimality of foraging behaviour (independent to any systematic bias to remain in patches longer – **Supplemental Figure 1**). Firstly, as the background environment varies (poor vs rich), the reward rate at leaving a given patch-type should differ by this same amount. Secondly, foragers should adjust their leaving time as patch quality varies, such that the instantaneous reward at leaving is the same in each patch (for a given background environment). That is within an environment, each patch should be left, regardless of its yield, when the rate at which milk is being accrued is the same. Strikingly, participants varied their leaving times as background environment changed, such that the difference in reward rate between the two conditions was very close to the actual difference in background reward rates (mean difference in reward rate at leaving = 3.33, actual difference between environments if behaving optimally = 3.30, $t_{38} = 0.07$, $p = 0.95$, **Figure 2C & 2D**). In contrast, the foreground reward rate at patch leaving did vary across patch type (RM-ANOVA $F(1.5,42) = 6.73$, $F = 6.73$, $p = 0.005$). Although the instantaneous reward rate on leaving low and medium yield patches did not differ (mean difference = 0.06, $t_{37} = 0.2$, $p = 1$), participants remained in high yield patches until the instantaneous reward rate was lower compared to both medium yield (mean difference = 1.1, $t_{37} = 3.8$, $p = 0.002$), and low yield patches (mean difference = 1.1, $t_{37} = 2.6$, $p = 0.04$; **Figure 2C**).

Thus, participants' sensitivity to changes in foraging parameters was close to optimal predictions, adjusting leaving times in response to changes in their background environment to closely match the actual changes in background reward rate. They also adjusted their leaving behaviour such that the reward rate at leaving did not differ between low and medium yield patches, although they tended to leave high yield patches later (i.e. after patch reward rate had dropped further).

Cabergoline alters the use of background reward information to guide patch leaving

Having demonstrated that healthy human patch leaving behaviour is aligned with the predictions of MVT, particularly in response to changes in background reward rate, we next examined whether dopamine modulates the effect of background reward rate (environment) on patch leaving behaviour. Using a within-subjects design, leaving times for 29 healthy, elderly people on placebo or following administration of the D2 receptor agonist cabergoline (which stimulates post-synaptic D2 receptors (36)) were analysed using a LME model. There was a significant interaction between drug state and the effect of background reward rate on leaving time ($F(1,200) = 5.22$, $p = 0.023$, **Supplementary Table 1B**). When ON cabergoline, people were less sensitive to the difference between poor and rich environments than when OFF drug (i.e. on placebo), even though they still showed a significant effect of background environment both ON and OFF the drug (**Figure 3A & C**).

We hypothesised that modulating dopamine levels would not alter the effect of foreground reward rate on patch leaving, if manipulating tonic levels predominantly effects the processing of average reward rates. In line with this hypothesis, there was no significant drug × patch interaction ($F(1,187) = 1.29$, $p = 0.26$): cabergoline did *not* lead to a significant change in the way participants used foreground reward rate information to guide leaving decisions (**Figure 3B**). There was also no statistically significant difference in leaving times overall on drug compared to placebo (mean difference = 0.73s, $F(1,29) = 1.86$, $p = 0.18$), nor did the reward rate at leaving vary as a function of drug state (mean difference = 0.39, $t_{28} = 0.8$, $p = 0.41$; **Figure 3D**).

The observed drug × background reward rate interaction was present across all patch types, with no 3-way interaction ($F(1,186) = 0.31$, $p = 0.58$). All of these results remain after controlling for weight, height, BMI and also for any effects of learning (s**ee Supplemental material: control analyses**). Additionally, the main effects reported in study 1 were replicated in this study of elderly healthy people, with both foreground (patch) and background (environment) reward rates significantly influencing patch leaving time, and no interaction between the two (Foreground: $F(1,57) = 425$, $p < 0.0001$**;** Background: $F(1,28) = 16.9$, $p = 0.0003$; Foreground x Background: $F(1,197) = 0.03$, $p = 0.86$; **Figure 3A and 3B**).

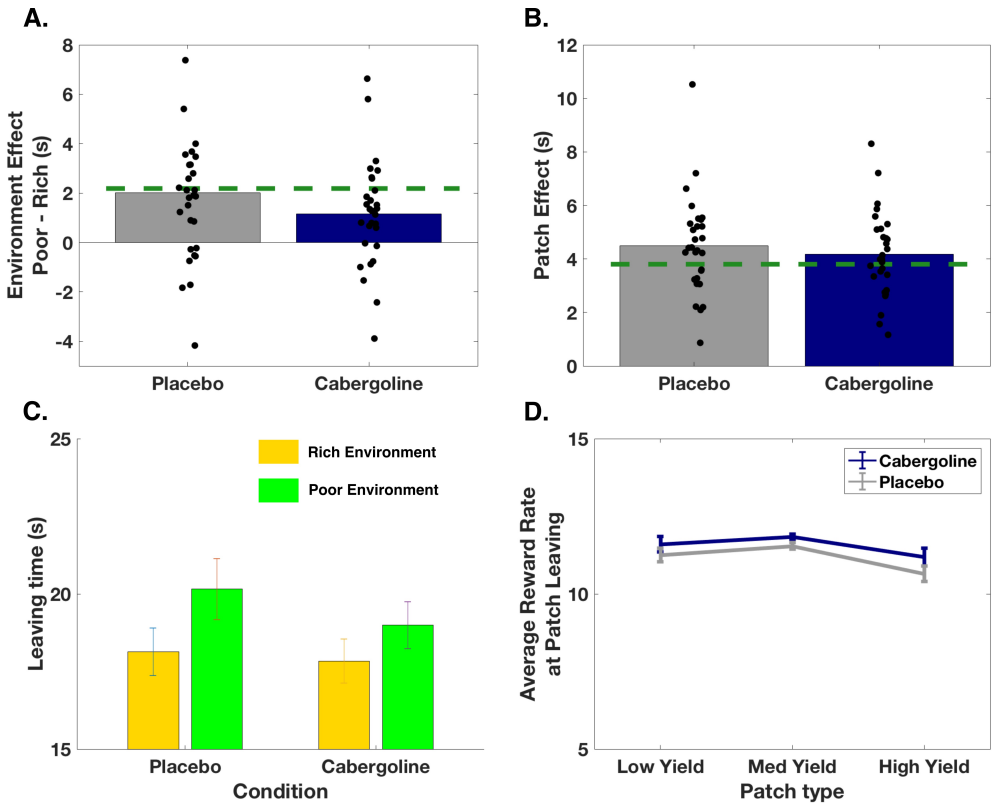

Fig 3. Cabergoline alters use of background reward information to guide patch leaving (**A**) There was a significant interaction between drug and background (environment) reward rate on leaving time, with a reduced effect of background environment ON cabergoline compared to OFF ($p = 0.023$). *Green dotted lines in (A) and (B) represent the predicted magnitude of effect of the manipulation, based on the marginal value theorem*. (B) In contrast, there was no significant interaction between drug and the effect of foreground (patch) reward rate on patch leaving ($p = 0.26$). (**C**) Raw leaving times for the two groups, in rich (gold) and poor (green) environments (collapsed across patch-type). The reduced effect of drug seemed mainly driven by participants ON cabergoline leaving patches earlier – and therefore when the patch reward rate was higher – in poor environments. (**D**) There was no main effect of cabergoline on either the instantaneous reward rate at patch leaving, or on raw leaving times (not shown) when collapsing across environments. N = 29, comparisons are within-subject, error bars are ± SEM.

Could participants be paying less attention when off medication? We analysed leaving time variability to examine whether participants' decisions were more noisy as a function of drug state. There was no significant difference in the variance of each participant's decisions between placebo and cabergoline conditions (Mean Difference $_{\text{PLAC-CAB}} = 0.31$, $t_{28} = 1.34$, $p = 0.19$ – **Supplemental Figure 3**).

Therefore cabergoline had a specific rather than general effect on patch leaving behaviour, altering only the influence of background reward rate on leaving time. This suggests that manipulating dopamine levels in healthy people alters patch leaving decisions by modulating sensitivity to average reward rates.

Dopamine and apathy influence the effect of reward context in Parkinson's disease

Previous evidence implicates dysfunction of the mesolimbic dopaminergic system in PD apathy (29,30,37). We hypothesised that this observation might be underpinned by reduced dopamine levels leading apathetic patients to chronically underestimate the (background) reward environment, and therefore not switch from their current behavioural states (even if these are minimal or effectively inertial). Consistent with this prediction, we found a significant 3-way interaction between background reward rate, being ON vs OFF dopaminergic medication and whether patients were apathetic or not ($F(1,200) = 7.03$, $p = 0.009$, **Supplementary Table 1C**). Specifically, dopamine altered the behavioural effect of the environment in patients with apathy, but not in those who were not apathetic.

In the OFF dopamine drug state apathetic PD patients showed a *reversal* of the expected effect of background environment on patch leaving time, leaving *earlier* in poor environments than in rich ones (**Figure 4A & B**). However, in the ON dopamine state their leaving decisions were not significantly different from predicted optimal behaviour, leaving patches later when background environment was *poorer* (change in environmental effect ON-OFF: $t_{17} = 2.24$, $p = 0.038$). In contrast, changing dopamine levels did not alter the effect of environment on patch leaving time in non-apathetic patients (change in environmental effect ON-OFF: $t_{16} = 0.31$, $p = 0.76$). Compared to HC, the effect of environment trended towards being significantly different from the PD apathy OFF group, and was not significantly different from the PD apathy ON group or either PD non-apathetic group; [Mean environment effect: HC = 0.5s, PD apathy ON = 0.5s, PD apathy OFF = -1.2s, PD no apathy ON = -0.1s, PD no apathy OFF = -0.5s; post-hoc unpaired t-tests: HC vs PD Ap-ON: $t = 0.03$, $p = 0.98$; HC vs PD Ap-OFF: $t = 1.84$, $p = 0.07$; HC vs PD NoAp-ON: $t = 0.54$, $p = 0.59$; HC vs PD NoAp-OFF: $t = 1.07$, $p = 0.29$].

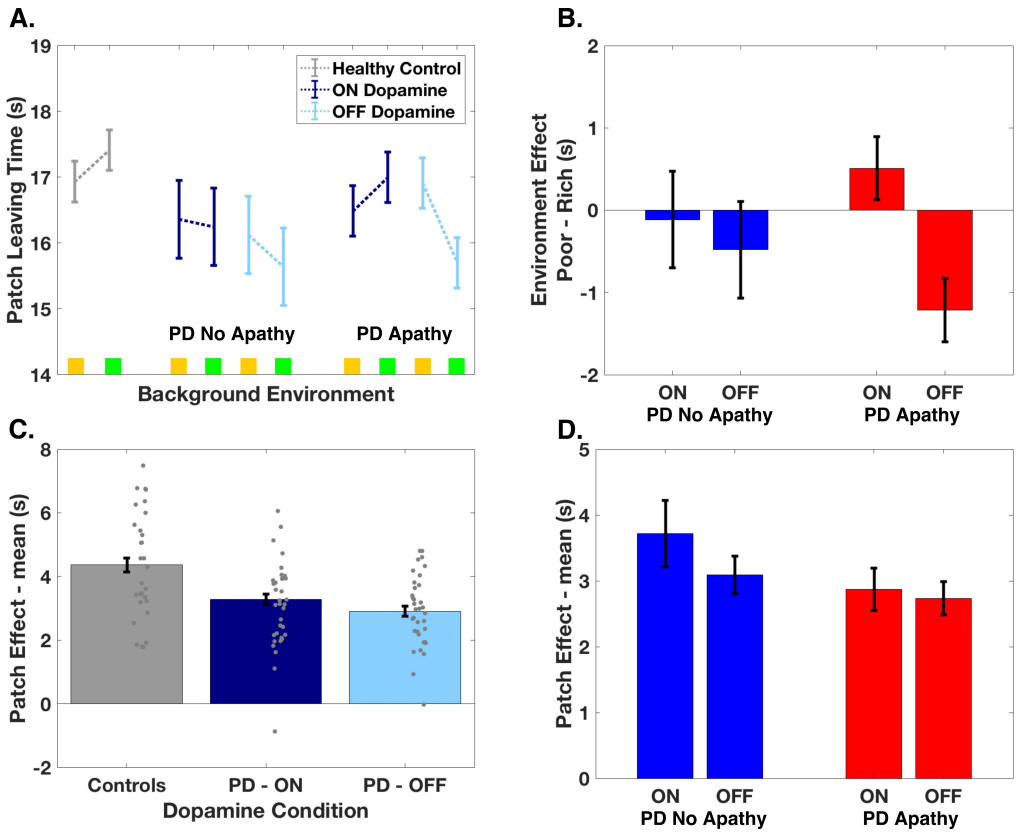

Fig 4. Dopamine changes influence of background environment dependent on motivational state

(**A**) There was a significant interaction between background reward rate, dopamine and apathy (p=0.009). Raw leaving times in each environment (rich and poor – gold and green boxes respectively), collapsed across patch-type, are shown for non-apathetic (N = 17) and apathetic (N = 18) PD patients, in the ON and OFF states, as well as the healthy control group (N = 29). There was no main effect of dopamine or apathy on leaving time. (**B**) Dopamine specifically changed the influence of background reward environment on switching behaviour, but only in the patients with apathy (ON vs OFF paired T-test, PD Apathy group: p = 0.038; PD No Apathy group: p = 0.76). (**C & D**) There was no interaction between dopamine, apathy and the influence of foreground reward rate on patch leaving (p=0.58). Parkinson's disease was associated with a significantly reduced effect of foreground reward rate on leaving time, independent of dopamine condition (**C** – Unpaired T-test Control vs PD-ON: p = 0.016; Control vs PD-OFF: p = 0.0001; PD-ON vs PD-OFF: p = 0.29) or apathy status (**D** – ON vs OFF paired T-test, PD Apathy group: p = 0.6; PD No Apathy group: p = 0.31). Error bars are ± SEM.

In the PD group as a whole, background environment alone did not have a significant main effect on patch leaving time (F(1,35) = 1.21, p = 0.28) – instead its effects depended on both drug and motivational state. These significant effects remained when controlling for potential effects of learning or attention (**Supplemental material – control analyses**). They suggest that low motivational states present in some PD patients – those with pathological apathy – mediate impairments in the use of background, but not foreground reward information.

Furthermore, these can be recovered through dopamine interventions, suggesting a dopaminergic origin for the effects of background reward rate.

Parkinson's disease but not dopamine or apathy reduced sensitivity to foreground rewards

As in the healthy control population, foreground (patch) reward rate strongly predicted leaving times ($F(1,68) = 252$, $p < 0.0001$, **Supplementary Table 1C**). However, neither change in dopamine state or baseline motivation affected the degree this variable influenced patch leaving behaviour (patch × DA: $F(1,188) = 1.02$, $p = 0.31$; patch × apathy: $F(1,68) = 2.26$, $p = 0.14$; **Figure 4C & D**). In contrast, the magnitude of the patch effect was reduced as a function of disease, with PD patients – whether ON or OFF their dopaminergic drugs – showing reduced sensitivity to this metric compared to HCs; [Mean patch effect: HC = 4.4s, PD-ON = 3.3s, PD-OFF = 2.9s; one-way ANOVA (group effect) $F(2,96) = 7.41$, $p = 0.001$. Post-hoc t-tests: HC vs PD-ON: MD = 1.1s, $t = 2.48$, $p = 0.016$; HC vs PD-OFF: MD = 1.5s, $t = 4.12$, $p = 0.0001$; PD-ON vs PD-OFF: MD = 0.38s, $t = 1.06$, $p = 0.29$].

No general effects of motivation and dopamine on patch leaving

Neither dopamine nor apathy had independent main effects on patch leaving time ($F(1,35) = 0.09$, $p = 0.77$ & $F(1,35) = 0.12$, $p = 0.73$ respectively; **Supplementary Table 1C**). There was also no two-way interaction between dopamine and motivational state ($F(1,35) = 0.003$, $p = 0.96$), nor were other two-way, three-way or the full four-way interactions significant. Furthermore, as with the Cabergoline study, the dopaminergic manipulation was not associated with a change in variance of patch leaving decisions ($MD_{ON\text{-}OFF} = 0.25$, $t_{34} = 1.25$, $p = 0.22$; **Supplemental Figure 3**), nor did this metric differ with apathy status (One-way ANOVA: $F(2,61) = 1.1$, $p = 0.34$, **Supplemental Figure 3).**

Therefore, PD patients show a general reduction in sensitivity to foreground rewards, but this does not depend on dopamine levels or apathy. In contrast, dopamine specifically alters the use of background rewards rates in apathetic PD patients when they make decisions to 'move on', without changing the influence of foreground reward rates, or causing a more general (and non-specific) shift in behaviour.

DISCUSSION

When to move on and leave a specific rewarding activity or location is an essential decision problem for animals and humans alike. In this set of studies we elucidate a cognitive mechanism which underpins how people use reward information to decide when to move on, and the neurotransmitter system supporting such decisions. Specifically, dopamine is an important contextual signal for knowing when a location is sufficiently bad or alternatives sufficiently good to move on. Additionally, we demonstrate that in a disease that involves dopaminergic systems (PD), disabling motivational deficits are associated with problems in utilising background reward rate information to drive patch leaving, which can be recovered through dopamine interventions.

The results provide new evidence for the role of dopamine in decision-making. Specifically, manipulation of dopamine levels modulated the influence of background – but not foreground – reward rate on dynamic decisions about when to switch behaviour (**Figures 3 and 4**). Although we do not explicitly measure firing rates of dopamine neurons, the drug manipulations used putatively alter tonic dopamine levels (36), a component of the dopaminergic neuromodulatory system which has been ascribed, in the context of motor responses, a crucial although at times controversial role in signalling background reward rates (1,19,22). Although some existing evidence suggests tonic dopamine levels encode information about background reward rate, and therefore the opportunity cost (alternatives that are foregone) of chosen actions (19,21), others have argued it encodes a more specific signal for the value of a current action, independent of environmental context (22). Here, we show that changing dopamine levels modulates the effect of background reward rates, not on actions *per se*, but rather on the more abstract decision of when to move on within an environment. Crucially, changes in dopamine tone did not alter the influence of foreground reward rate on patch leaving, nor did the variance of participants' decisions change with drug state. The results were therefore specific to a component of the context in which rewards are being accrued (background reward rate), and could not be explained by a confounder such as altered attention as a function of drug. They accord with work suggesting that mesolimbic dopamine plays a role in the trade-off between exploring and exploiting currently available instrumental rewards (38–40), a situation that can also be understood within a MVT framework (17). These findings place tonic dopamine at the core of how foraging decisions are made. Furthermore, although dopamine levels in the PD patients were mainly altered via

transient withdrawal of levodopa-containing medications, the specificity of cabergoline for D2 receptors suggests D2-mediated pathways may be of particular importance for signalling contextual reward information (41).

The results presented here also reveal a precise cognitive mechanism by which dysfunction of dopaminergic systems could lead to apathy (**Figure 4**). A role for dopamine as a contextual signal of background reward rate, thus influencing 'exploration' behaviour, has clear appeal as a mechanistic account of apathy (27). Simply, the hallmark of apathetic behaviour – reduced goal-directed activity – may occur because of an impaired ability to estimate or utilise information about background reward rates, impeding switching behaviour from a current activity (even if this activity is very minimal). Apathy is a common and debilitating complication of many neurological and psychiatric conditions, and has been associated with disrupted reward systems across many disorders – including Parkinson's disease (3,8,31,32,42), cerebral small vessel disease (43) and schizophrenia (44). An abundance of evidence links dopaminergic systems to the processing of rewarding outcomes, encoding the value of potential actions and motivating behaviours towards goals (1–3,7,12,18,45). However, evidence to date suggests that – in tasks where reward is treated as a single construct – dopamine exerts its influence on behaviour in a dissociable manner to apathy (8,31).

Here, the results demonstrate a specific interaction between apathy and the effect of background reward rate on patch leaving decisions, as a function of dopaminergic tone. In the OFF state, apathetic patients showed a *reversal* of the predicted effect of background reward rate (23), persisting in patches for longer when environmental reward rates were higher. This behaviour is not consistent with patients simply estimating environmental reward rate as lower, but rather suggests a failure to utilise available information about reward context to appropriately guide decisions. Consistent with the main hypotheses of this study, dopamine restored apathetic (but not non-apathetic) patients' behaviour to the predicted direction (leaving patches earlier in rich compared to poor environments). In contrast, neither dopamine state nor apathy altered the influence of foreground reward rate on patch leaving, which instead varied as a function of disease. Overall, this offers a new interpretation of the relationship between reward and apathy. Specifically, apathetic patients used background reward information mal-adaptively to guide decisions of when to move on, dependent on baseline dopamine levels. This result is consistent with the hypothesis that disrupted

representation of background reward rate – or opportunity cost – contributes to apathy in PD, whilst suggesting a potential role for dopamine in ameliorating this deficit. More generally, it demonstrates a novel component of cost-benefit decision making which may be disrupted in apathy, further advancing understanding of this debilitating clinical syndrome (27).

Our results also highlight that human behaviour in an ecologically-derived decision making task is closely described by a normative model based on the principles of the marginal value theorem (**Figure 2**) (14,24). This accords with earlier field work in behavioural ecology (14,23) and anthropology (46,47) literatures, and more recent work beginning to explore the neural basis of such decisions (35). In the current study, the use of a foraging framework informed by MVT enabled us to dissociate the effects of reward rates on different time scales, in a way that is not possible in reinforcement-learning based manipulations of average reward rates, where the receipt of an instrumental reward instantaneously increases average reward rate (15,19). Here, participants utilised these dissociable aspects of their reward environment to adjust patch leaving behaviour in close to an optimal fashion, as both foreground and background reward rates varied. This provides evidence for a common decision principle guiding foraging-style behaviour in both humans and other animals, and allows further investigation of the specific neural mechanisms underlying it.

Although the effects of changing dopamine levels were specific to background reward rate across studies, a differing pattern of effect on how this information altered patch leaving decisions was observed between the cabergoline manipulation in healthy people, and dopamine medication manipulation in apathetic patients with PD. One explanation for such opposing effects is that whilst the ON state in PD patients is associated with increased dopaminergic tone (as demonstrated by reduced motor disability scores – **Table 1**), the relatively low dose of cabergoline administered to healthy participants could theoretically, via actions on pre-synaptic D2 autoreceptors, reduce tonic dopamine (48–50). An alternative possibility is suggested by past research examining the effects of dopamine on cognitive control, which has highlighted an inverted-U shaped function, characterised by detrimental effects on behaviour if tonic dopamine levels are too high or too low (51). Our results are consistent with such an inverted U-shaped function. Apathetic PD patients, in whom previous work has demonstrated reduced levels of dopamine (30,37), show a lack of ability to appropriately process average reward rates when OFF their medication, but are restored – and closer to optimal – when on their medication (**Fig 4**). However, healthy individuals show

reduced sensitivity to changing background reward rates when their tonic dopamine levels are (putatively) boosted on cabergoline compared to placebo. Thus, people who have typical dopaminergic function become poorer at utilising information about reward context when their dopamine levels are boosted, while conversely dopamine medications restore the performance of apathetic PD patients back towards normal.

Irrespective of the exact pharmacological mechanism underlying our observations, the experiments presented here demonstrate a robust, consistent effect of dopamine on the responsiveness to background reward rate, modulated in the last study by apathy status. Importantly, variance in patch leaving times did not change as a function of dopamine or apathy state. This, along with the specific rather than general changes in behaviour we observed, make it unlikely in our opinion the observed results can be explained by a confounding factor such as reduced attention or motor disturbance in the OFF state. Furthermore, the use of a continuously changing patch gain function, rather than stepped changes as has been used in previous studies (52,53) minimised the use of simple heuristics to guide decisions while having the statistical advantage of leaving the dependent variable approximately normally distributed. The experimental design, grounded in MVT, allowed for a direct comparison of behaviour against normative predictions, predictions that have previously shown to hold in animals both freely foraging in the wild, and within controlled experimental setups (26,35,54).

Recent theoretical accounts of decision making have called for a shift to more ecologically derived experiments to investigate the mechanisms of this fundamental neural process (14,15). The current results highlight the utility of such an approach. They demonstrate the applicability of a normative model validated in wild and experimental animal populations to human behaviour in health and disease. They link basic ecological models of animal behaviour to a mechanistic understanding of human decision making, highlighting the specific influence of dopaminergic systems as people decide when to move on as they pursue rewards in their environment. Furthermore, they demonstrate the translational potential of such ecologically derived approaches to understanding complex neuropsychiatric syndromes, here showing how pathological disruption of an underlying cognitive process is associated with the clinical consequence of apathy. Together, the results bring us closer to a mechanistic understanding of motivated behaviour in health and disease, demonstrating the utility of

ecological approaches for advancing understanding of normal and abnormal human behaviour.

MATERIALS AND METHODS

We performed three experiments aimed at identifying whether (i) humans make patch leaving decisions in line with MVT, (ii) modulating dopaminergic systems with the D2 receptor agonist cabergoline specifically alters people's sensitivity to the background reward rate and (iii) whether apathetic PD patients show a differential effect of dopaminergic medication on background reward sensitivity compared to non-apathetic PD patients.

Participants

This study was approved by Oxford University Hospitals Trust ethics committee and written informed consent was obtained from all participants.

Experiment ONE (healthy people): 40 healthy volunteers (mean age 24, range 20-30) were recruited via a local database. One was subsequently excluded because of poor engagement with the task (identified at a de-briefing interview).

Experiment TWO (cabergoline): 30 healthy elderly (mean age 69, range 60-78) participants were recruited via a local database. Potential participants were screened for the presence of neurological, psychiatric or cardiovascular diseases, or for the use of medications that could interact with Cabergoline, and excluded if any of these were present. One subject was subsequently excluded because a core metric of task performance (variance in leaving times per condition) fell outside three standard deviations of the mean variance, leaving 29 participants for analysis.

Experiment THREE (Parkinson's Disease): 36 patients with a clinical diagnosis of idiopathic Parkinson's disease (PD), confirmed independently by two neurologists, were recruited from local movement disorders clinics in the Oxfordshire area. Inclusion criteria included an absence of PD dementia or other major neurological or psychiatric conditions. Patients with clinical apathy were intentionally recruited, such that the study recruitment had an equal split of apathetic and non-apathetic patients. One patient was subsequently excluded due to failure to understand the task and decisions that fell outside of 3 standard deviations from the group

mean, leaving 35 patients. A separate cohort was also recruited from the local Oxfordshire region as a gender and age matched control group for the PD patients. This group was free from cognitive impairment or apathy. Two were subsequently excluded because of concerns about their task performance (not engaging with the task, identified at post-test debriefing), leaving a total of 29 participants.

Demographics of participants are presented in **Table** 1.

Questionnaire and Baseline Cognitive Measures

Apathy was assessed by standardised clinical interview with the patient, using the Lille apathy rating scale (LARS – range -36 to 36), which has previously been validated in PD (55). Patients were classified as apathetic if their LARS score was > -22 (a cut-off corresponding to at least mild-moderate apathy levels). Severity of PD was assessed using the Unified PD rating scale (UPDRS) total score (56) and Hoehn and Yahr stage. The UPDRS-III (motor score) was repeated in the ON and OFF states. As a baseline cognitive screen, all subjects were administered the Addenbrooke's cognitive examination version III (ACE-III) (57), and a digit span task to assess working memory (58), in the ON state. Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II) (59).

Measure	Cabergoline study participants	Healthy elderly controls (PD study)	Parkinson's disease	Control vs Parkinson's disease (p value)	Parkinson's disease – no apathy (LARS ≤ -22)	Parkinson's disease – apathy (LARS >-22)	No apathy vs apathy (p value)
Number	29	29	35	n/a	17	18	n/a
Age	68.2 (±4.5)	68.6 (±8.2)	67.7 (±8.0)	p=0.66	68.4 (±6.7)	67.2 (±9.2)	p=0.67
Gender (F/M)	11/18	10/18	11/24	p=0.79^	7/10	4/14	p=0.29^
Apathy (LARS)	-21.4 (±4.5)	-26.7 (±4.1)	-21.1 (±6.5)	**P=0.0002**	-26.7 (± 3.7)	-15.9 (±3.3)	**p<0.0001**
Hoehn & Yahr stage	n/a	n/a	2.2 (±0.5)	n/a	2.2 (±0.5)	2.1 (±0.5)	p=0.83
UPDRS - total	n/a	n/a	83.6 (25.4)	n/a	75.2 (±25.9)	91 (±23.2)	p=0.08
UPDRS motor score ON	n/a	n/a	29.1 (±11.4)	n/a	27.9 (±13.1)	30.3 (±9.8)	p=0.55
UPDRS motor score OFF	n/a	n/a	36.0 (±10.4)	n/a	32.8 (±11.3)	39.1 (±8.7)	p=0.07
Change in motor score	n/a	n/a	6.9 (±8.0)	n/a	4.8 (±7.8)	8.8 (±8.0)	p=0.14
Levodopa equivalent dose (mg/24 hours)	n/a	n/a	621 (±356)	n/a	534 (±339)	702 (±363)	p=0.17
Hours since last dose – OFF	n/a	n/a	18 (±3)	n/a	19 (±3)	17 (±3)	p=0.07
Hours since last dose – ON	n/a	n/a	2.3 (±1.5)	n/a	2.7 (±1.6)	1.8((±1.5)	p=0.11
Depression (BDI-II)	n/a	3.9 (±3.9)	14.5 (±7.9)	**p<0.0001**	11.3 (±7.0)	17.4 (±7.7)	**p=0.02**
Dysphoria sub-scale	n/a	(1.2±1.6)	(5.0±4.1)	**p<0.0001**	(4.5±4.1)	(5.6±4.1)	p=0.43
Global Cognition (ACE)	97.5 (±2.9)	95.7 (±3.7)	90.7 (±8.2)	**p=0.004**	93.5 (±5.1)	88.2 (±9.8)	p=0.06
Digit span	19.4 (±3.8)	21.2 (±4.5)	17.1 (±3.6)	**p=0.0002**	16.7 (±3.1)	17.5(±4.1)	p=0.57

Table 1. Demographics of participants in experiment two and three

LARS – Lille apathy rating scale; UPDRS – Unified Parkinson's disease rating scale; BDI-II – Beck's depression inventory II; ACE – Addenbrooke's cognitive examination III; ^chi-squared test; (all values are mean +/- standard deviation)

Patch Leaving Paradigm

The aim of this design was to independently manipulate background and foreground reward rates based on the principles of marginal value theorem, a theory of optimal foraging in patch leaving (23,24) – see **Supplemental Figure 1**. The experiment was designed as a patch leaving problem, with participants aiming to maximise their overall reward returns by deciding how long to spend in sequentially encountered patches. In each patch, participants obtained rewards at an exponentially decrementing rate. Moving to a new patch, which they were free to do at any point, incurred a fixed time delay of six seconds, during which no reward could be gathered. The experiment lasted a fixed amount of time (10 minutes per environment type), however a potentially unlimited number of patches were available.

Foreground reward rate was determined by the patch reward function. Three patch-types were used, differing in the scaling factor of the reward function (***S*** in equation one below), and corresponding to low (32.5), medium (45) and high (57.5) yield patches. The foreground reward rate, after ***T*** seconds in a patch, was determined by the equation:

$$\boldsymbol{g'(T) = S * e^{-0.075*T}} \quad \textbf{(1)}$$

Background reward rate was manipulated by varying the proportions of low, medium and high yield patches. Two environments were used: a rich environment in which 50% of the patches were high yield, 30% medium and 20% low yield, and a poor environment in which 50% of the patches were low yield, 30% medium and 20% high. Therefore, the background reward rate was higher in the rich environment. MVT demonstrates that, to maximise reward gain, participants should leave each field when the instantaneous reward rate in the field (from **equation 1**) drops below the background average reward rate for the farm (determined by the environment type; **Supplemental figure 1)**. Simply, for a given patch-type, participants should leave earlier in the rich environment compared to the poor environment (**Figure 1C**).

To improve engagement, the task was framed in a 'real-world' farmyard setting. Each patch was a field of cows returning milk, displayed on the monitor as a bucket that continuously filled during patch residency. The height of milk displayed in the bucket was proportional to the integral of equation (1) between time = 0 and T, and was updated with a frequency of 20Hz. The rate of filling declined according to **equation 1**. Thus the rate of milk yield

indicated the foreground reward rate. Participants were not explicitly told which patch-type they were currently in – rather they inferred this by observing the rate of milk accumulation. The background reward rate was continuously cued by the coloured border on the screen, indicating either the rich (gold border) or poor farm (green border). When participants chose to leave their current patch (by releasing the spacebar they had been holding down), they incurred a fixed time cost of 6 seconds, described as the time to walk to the next patch. During this time a counter was displayed which ticked down the seconds until the next patch was reached. On arriving at the next patch participants were cued to "press and hold the spacebar", and after doing this the screen display changed to show the new patch.

Procedure

Before commencing the experiment participants were trained on the task elements via a structured explanation and practice session lasting approximately 20 minutes. Comprehension of the different elements was checked verbally before commencing the main experiment, with participants asked to explain what each display item meant. Participants were not given any instructions as to what optimal behaviour would be. They were told they would spend an equal amount of time on the two farm types (gold and green) and that they would never run out of fields. Participants were seated in front of a desktop computer running Pyschtoolbox (pyschtoolbox.org) implemented within MATLAB (MathWorks, USA).

Experiment ONE: Participants were tested in a single session following training as above.

Experiment TWO: This experiment was conducted as a randomised, double-blind, placebo-controlled experiment. Participants were tested in two separate sessions, once following administration of a single dose of 1mg Cabergoline, and once following administration of an indistinguishable placebo tablet. The order of testing was counterbalanced across drug manipulation, gender and order of background foraging environment (rich-poor or poor-rich).

Experiment THREE: The Parkinson's disease patients were tested in two separate sessions – once ON their normal dopaminergic medications, and once following an overnight withdrawal of these drugs (OFF). The order of testing was counterbalanced across apathy status and order of background foraging environment.

Statistical analysis

We used a hierarchical linear mixed effects model (*fitlme* in MATLAB, Mathworks, USA; maximum likelihood estimation method) as our primary analysis method for all three experiments, to account for between and within subject effects. All fixed effects of interest (patch, environment and where applicable dopamine and apathy) and their interactions were included, and the random effects structure was determined by systematically adding components until the Akaike Information Criterion was minimised (60). Notably the reported effects in all these models were also present in the simpler models fitting only a random effect of subject.

Experiment ONE:

$$Leaving\ Time = 1 + patch * env + (1|\text{sub}) + (1|\text{sub:patch}) + (1|\text{sub:env}) + (1|\text{sub:patch:env})$$

Experiment TWO:

$$Leaving\ Time = 1 + patch * env * DA + (1|\text{sub}) + (1|\text{sub:DA}) + (1|\text{sub:patch}) + (1|\text{sub:env}) + (1|\text{sub:patch:env:DA})$$

Experiment THREE:

$$Leaving\ Time = 1 + patch * env * DA * Ap + (1|\text{sub}) + (1|\text{sub:DA}) + (1|\text{sub:patch}) + (1|\text{sub:env}) + (1|\text{sub:patch:env:DA})$$

patch = foreground reward rate, env = background reward rate, DA = dopamine state, Ap = Apathy status sub = subject.
Fixed effects are shown in blue, random effects in green.

To avoid the potentially biasing effects of outlying data points on the primary analysis we excluded, subject by subject, any trials in which the leaving time was more than 3 standard deviations above that individual's mean leaving time. Of note, this approach did not change the significance (or otherwise) of any reported results compared to analysis of the full data set.

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AUTHOR CONTRIBUTIONS

CLH, NK, MH and MAJA designed the study; CLH, NK and MAJA coded the experiment, CLH, OP, AK, RJ and YA collected data; CLH, NK, SF and MAJA analysed data; CLH, NK, SF, MH and MAJA wrote the paper.

DECLARATION OF INTERESTS

We declare no conflicts of interest.

REFERENCES

1. Hamid AA, Pettibone JR, Mabrouk OS, Hetrick VL, Schmidt R, Vander Weele CM, et al. Mesolimbic dopamine signals the value of work. Nat Neurosci. 2016 Jan;19(1):117–26.
2. Salamone JD, Correa M. The Mysterious Motivational Functions of Mesolimbic Dopamine. Neuron. 2012;76(3):470–85.
3. Le Bouc R, Rigoux L, Schmidt L, Degos B, Welter M-L, Vidailhet M, et al. Computational Dissection of Dopamine Motor and Motivational Functions in Humans. J Neurosci. 2016 Jun 22;36(25):6623–33.
4. Haber SN, Knutson B. The Reward Circuit: Linking Primate Anatomy and Human Imaging. Neuropsychopharmacology. 2010 Jan 7;35(1):4–26.
5. Manohar SG, Chong TT-J, Apps MAJ, Batla A, Stamelou M, Jarman PR, et al. Reward Pays the Cost of Noise Reduction in Motor and Cognitive Control. Curr Biol. 2015 Jun 29;25(13):1707–16.
6. Schultz W, Dickinson A. Neuronal Coding of Prediction Errors. Annu Rev Neurosci. 2000 Mar;23(1):473–500.
7. Syed ECJ, Grima LL, Magill PJ, Bogacz R, Brown P, Walton ME. Action initiation shapes mesolimbic dopamine encoding of future rewards. Nat Neurosci. 2016 Jan;19(1):34–6.
8. Le Heron C, Plant O, Manohar S, Ang YS, Jackson M, Lennox G, et al. Distinct effects of apathy and dopamine on effort-based decision-making in Parkinson's disease. Brain. 2018;141(5):1455–69.
9. Schultz W. Dopamine reward prediction-error signalling: a two-component response. Nat Rev Neurosci. 2016 Mar;17(3):183–95.

10. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature. 2006 Aug 23;442(7106):1042–5.
11. Salamone JD, Correa M, Farrar A, Mingote SM. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology (Berl). 2007;191(3):461–82.
12. Howe MW, Tierney PL, Sandberg SG, Phillips PEM, Graybiel AM. Prolonged dopamine signalling in striatum signals proximity and value of distant rewards. Nature. 2013 Aug;500(7464):575–9.
13. Mohebi A, Pettibone JR, Hamid AA, Wong J-MT, Vinson LT, Patriarchi T, et al. Dissociable dopamine dynamics for learning and motivation. Nature. 2019 May 22;1.
14. Pearson JM, Watson KK, Platt ML. Decision making: The neuroethological turn. Neuron. 2014;82(5):950–65.
15. Mobbs D, Trimmer PC, Blumstein DT, Dayan P. Foraging for foundations in decision neuroscience: insights from ethology. Nat Rev Neurosci. 2018 Jul 11;19(7):419–27.
16. Rutledge RB, Lazzaro SC, Lau B, Myers CE, Gluck MA, Glimcher PW. Behavioral/Systems/Cognitive Dopaminergic Drugs Modulate Learning Rates and Perseveration in Parkinson's Patients in a Dynamic Foraging Task. 2009;
17. Constantino SM, Dalrymple J, Gilbert RW, Varenese S, Rocco A Di, Daw N. A Neural Mechanism for the Opportunity Cost of Time. bioRxiv. 2017 Aug 8;173443.
18. Kurniawan IT, Guitart-Masip M, Dolan RJ. Dopamine and effort-based decision making. Front Neurosci. 2011;5(JUN):1–10.
19. Niv Y, Daw ND, Joel D, Dayan P. Tonic dopamine: opportunity costs and the control of response vigor. Psychopharmacology (Berl). 2007 Apr;191(3):507–20.
20. Beierholm U, Guitart-Masip M, Economides M, Chowdhury R, Düzel E, Dolan R, et al. Dopamine Modulates Reward-Related Vigor. Neuropsychopharmacology. 2013 Jul 18;38(8):1495–503.
21. Guitart-Masip M, Duzel E, Dolan R, Dayan P. Action versus valence in decision making. Trends Cogn Sci. 2014 Apr;18(4):194–202.
22. Zenon A, Devesse S, Olivier E. Dopamine Manipulation Affects Response Vigor Independently of Opportunity Cost. J Neurosci. 2016 Sep 14;36(37):9516–25.
23. Stephens DW, Krebs JR (John R. Foraging theory. Princeton University Press; 1986.
24. Charnov EL. Optimal foraging, the marginal value theorem. Theor Popul Biol. 1976 Apr;9(2):129–36.

25. Stephens DW, Brown JS (Joel S, Ydenberg RC. Foraging : behavior and ecology. University of Chicago Press; 2007. 608 p.
26. Nonacs P. State dependent behavior and the Marginal Value Theorem. Behav Ecol. 2001;12(1):71–83.
27. Le Heron C, Apps. MAJ, Husain M. The anatomy of apathy: A neurocognitive framework for amotivated behaviour. Neuropsychologia. 2018 Jul 8;118:54–67.
28. Le Heron C, Holroyd CB, Salamone J, Husain M. Brain mechanisms underlying apathy. J Neurol Neurosurg Psychiatry. 2019 Mar 1;90(3):302–12.
29. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain. 2005;128(6).
30. Santangelo G, Vitale C, Picillo M, Cuoco S, Moccia M, Pezzella D, et al. Apathy and striatal dopamine transporter levels in de-novo, untreated Parkinson's disease patients. Parkinsonism Relat Disord. 2015;21(5):489–93.
31. Muhammed K, Manohar S, Ben Yehuda M, Chong TT-J, Tofaris G, Lennox G, et al. Reward sensitivity deficits modulated by dopamine are associated with apathy in Parkinson's disease. Brain. 2016 Jul 24;
32. Martinez-Horta S, Riba J, de Bobadilla RF, Pagonabarraga J, Pascual-Sedano B, Antonijoan RM, et al. Apathy in Parkinson's Disease: Neurophysiological Evidence of Impaired Incentive Processing. J Neurosci. 2014 Apr 23;34(17):5918–26.
33. Thobois S, Lhommée E, Klinger H, Ardouin C, Schmitt E, Bichon A, et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. Brain. 2013 May;136(5):1568–77.
34. Adam R, Leff A, Sinha N, Turner C, Bays P, Draganski B, et al. Dopamine reverses reward insensitivity in apathy following globus pallidus lesions. Cortex. 2013;49(5):1292–303.
35. Hayden BY, Pearson JM, Platt ML. Neuronal basis of sequential foraging decisions in a patchy environment. Nat Neurosci. 2011;14(7):933-U165.
36. Brooks DJ, Abbott RJ, Lees AJ, Martignoni E, Philcox D V, Rascol O, et al. A placebo-controlled evaluation of ropinirole, a novel D2 agonist, as sole dopaminergic therapy in Parkinson's disease. Clin Neuropharmacol. 1998;21(2):101–7.
37. Thobois S, Ardouin C, Lhommee E, Klinger H, Lagrange C, Xie J, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. Brain. 2010 Apr 1;133(4):1111–27.

38. Kayser AS, Mitchell JM, Weinstein D, Frank MJ. Dopamine, Locus of Control and the Exploration-Exploitation Tradeoff. Neuropsychopharmacology. 2015 Jan 30;40(2):454–62.
39. Daw ND, O'Doherty JP, Dayan P, Seymour B, Dolan RJ. Cortical substrates for exploratory decisions in humans. Nature. 2006 Jun 15;441(7095):876–9.
40. Westbrook A, Frank M. Dopamine and proximity in motivation and cognitive control. Curr Opin Behav Sci. 2018 Aug 1;22:28–34.
41. Beaulieu J-M, Gainetdinov RR. The Physiology, Signaling, and Pharmacology of Dopamine Receptors. 2011;
42. Lawrence AD, Goerendt IK, Brooks DJ. Apathy blunts neural response to money in Parkinson's disease. Soc Neurosci. 2011 Oct;6(5–6):653–62.
43. Le Heron C, Manohar S, Plant O, Muhammed K, Griffanti L, Nemeth A, et al. Dysfunctional effort-based decision-making underlies apathy in genetic cerebral small vessel disease. Brain. 2018;141(11):3193–210.
44. Strauss GP, Waltz JA, Gold JM. A Review of Reward Processing and Motivational Impairment in Schizophrenia. Schizophr Bull. 2014 Mar 1;40(Suppl 2):S107–16.
45. Schultz W. Behavioral dopamine signals. Trends Neurosci. 2007;30(5):203–10.
46. Smith EA, Bettinger RL, Bishop CA, Blundell V, Cashdan E, Casimir MJ, et al. Anthropological Applications of Optimal Foraging Theory: A Critical Review [and Comments and Reply]. Curr Anthropol. 1983 Dec 19;24(5):625–51.
47. Metcalfe D, Barlow KR. A Model for Exploring the Optimal Trade-off between Field Processing and Transport. Vol. 94, American Anthropologist. WileyAmerican Anthropological Association; 1992. p. 340–56.
48. Chen Y-CI, Choi J-K, Andersen SL, Rosen BR, Jenkins BG. Mapping dopamine D2/D3 receptor function using pharmacological magnetic resonance imaging. Psychopharmacology (Berl). 2005 Aug 5;180(4):705–15.
49. Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience. 1991;41(1):1–24.
50. Pizzagalli DA, Evins AE, Schetter EC, Frank MJ, Pajtas PE, Santesso DL, et al. Single Dose of a Dopamine Agonist Impairs Reinforcement Learning in Humans: Behavioral Evidence from a Laboratory- based Measure of Reward Responsiveness NIH Public Access. Psychopharmacol. 2008;196(2):221–32.
51. Cools R, D'Esposito M. Inverted-U–Shaped Dopamine Actions on Human Working

Memory and Cognitive Control. Biol Psychiatry. 2011 Jun 15;69(12):e113–25.
52. Hutchinson JMC, Wilke A, Todd PM. Patch leaving in humans: can a generalist adapt its rules to dispersal of items across patches? Anim Behav. 2008 Apr;75(4):1331–49.
53. Constantino SM, Daw ND. Learning the opportunity cost of time in a patch-foraging task. Cogn Affect Behav Neurosci. 2015 Dec 28;15(4):837–53.
54. Krebs J, Erichsen J, Webber M, Charnov E. Optimal prey selection in the great tit. Anim Behav. 1977;(25):30–8.
55. Sockeel P, Dujardin K, Devos D, Denève C, Destée A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006 May 1;77(5):579–84.
56. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord. 2008 Nov 15;23(15):2129–70.
57. Hsieh S, Schubert S, Hoon C, Mioshi E, Hodges JR. Validation of the Addenbrooke's Cognitive Examination III in Frontotemporal Dementia and Alzheimer's Disease. Dement Geriatr Cogn Disord. 2013;36(3–4):242–50.
58. Groth-Marnat G. Neuropsychological assessment in clinical practice : a guide to test interpretation and integration. Wiley; 2000. 653 p.
59. Beck AT, Steer RA, Brown GK. Manual for the Beck depression inventory-II. San Antonio, TX Psychol Corp. 1996;1–82.
60. Barr DJ, Levy R, Scheepers C, Tily HJ. Random effects structure for confirmatory hypothesis testing: Keep it maximal. J Mem Lang. 2013 Apr;68(3).