

1                                    ***Dopamine and motivational state drive dynamics***  
2                                    ***of human decision making***

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## 1 **ABSTRACT**

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

21

## 22 **KEY WORDS**

23 Dopamine; Apathy; Decision making; Reward; Foraging; Opportunity cost;  
24 Parkinson’s Disease

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## 1 INTRODUCTION

2 The mesolimbic dopaminergic system plays a crucial role in motivating behaviour towards  
3 goals and has been closely linked to neural circuits which convey information about rewards  
4 (1–6). Several experiments across species have demonstrated a crucial role for dopamine in  
5 overcoming costs to obtain rewards (2,3,7,8) and for learning about reward outcomes to  
6 update future behaviour (9,10). Tasks probing dopamine function typically require an agent  
7 to make *binary decisions* between presented options, based on learning the contingent  
8 relationship between stimuli and rewards, or an integration of cost and reward information  
9 (8,9,11). However, animal models increasingly highlight that dopamine signals change  
10 during on-going behaviours and carry information that is not exclusively tied to reward  
11 predicting cues (1,12,13).

12

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

22

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

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

19  
20 From a clinical perspective, impairment of mechanisms underlying foreground/background  
21 decision making may underlie pathological apathy, a disabling disorder of motivated, goal  
22 directed behaviour (27). Apathy is a common feature of many psychiatric and neurological  
23 disorders, and identification of mechanisms underlying the syndrome remains a crucial  
24 challenge for development of effective treatments (28). In Parkinson’s disease (PD) it has  
25 been linked to alterations in mesolimbic dopaminergic systems (27,29,30), reduced  
26 physiological responses to rewards (31,32), and reduced willingness to exert effort for reward  
27 (3,8). Furthermore, apathy can be successfully treated in some patients with dopamine  
28 agonists, which selectively stimulate D2 and D3 receptors (33,34). A foreground/background  
29 decision making framework can potentially unite the above observations. If tonic dopamine  
30 levels signal background reward rate – a crucial contextual cue for when to switch behaviour  
31 – apathetic patients, in whom these dopamine levels are reduced, may be less inclined to  
32 switch from their current (foreground) activity, even if this activity involves doing very little.  
33 However, the relationship between dopamine, apathy and different components of reward  
34 (foreground and background) has never been examined.

1

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

14

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

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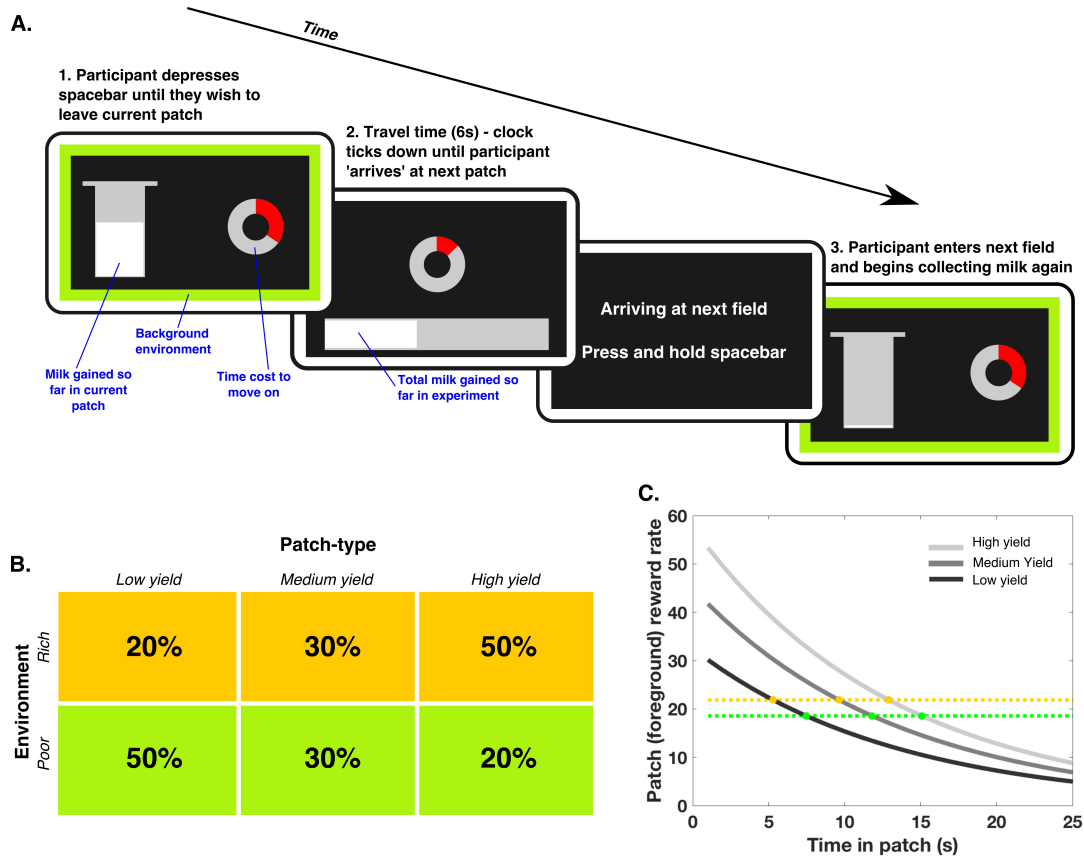
## 24 **RESULTS**

25 All participants were administered a computer based patch-leaving task in which they had to  
26 decide when to move on from a current patch. The task design specifically manipulated the  
27 background and foreground reward rates, in line with the predicted effects according to MVT  
28 (23,24).

29

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

1 decisions of whether to move on (leave the field for the next one) (**Figure 1**). Moving on to  
 2 the next field incurred a time cost of 6 seconds, during which no milk could be collected.  
 3  
 4 To manipulate the foreground reward rate, there were three field-types, which returned milk  
 5 at high, medium and low rates, which exponentially decayed over time in the field. The field-  
 6 type was indicated by the rate at which the bucket on the screen filled. The distribution of  
 7 these field-types within a “farm” determined the background reward rate.



10

### 11 **Figure 1. Patch leaving paradigm**

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

1 high yield), which determined the foreground reward rate. Two different background environments (farms) were  
2 used, with the background reward rate determined by the relative proportions of these patch-types. The gold  
3 farm contained a higher proportion of high yield fields, and a lower proportion of low yield ones, meaning it had  
4 a higher background reward rate than the green farm, which had a higher proportion of low yield fields. (C)  
5 According to MVT participants should leave each patch when the instantaneous reward rate in that patch (grey  
6 lines) drops to the background environmental average (gold and green dotted lines). Therefore, people should  
7 leave sooner from all patches in rich (gold dotted line) compared to poor (green dotted line) environments, but  
8 later in high yield compared to low yield patches. Crucially, these two effects are independent from each other.  
9

10 On the “rich” farm (signalled by a gold border on the screen) 50% of encountered fields were  
11 high yield, 30% were medium yield and 20% were low yield. On the “poor” farm (signalled  
12 by a green border) 50% of encountered fields were low yield, 30% medium and just 20%  
13 high yield. Thus, the background reward rate was lower on the green farm than the gold farm.  
14 Participants were aware that an unlimited number of fields were available to them, but for  
15 only a fixed amount of time. The influence of foreground and background reward rates, and  
16 where relevant dopamine and apathy, on patch leaving time was analysed using a linear  
17 mixed effects model (LME) – see **Methods** for further details.  
18

### 19 ***Healthy human foragers are guided by MVT principles***

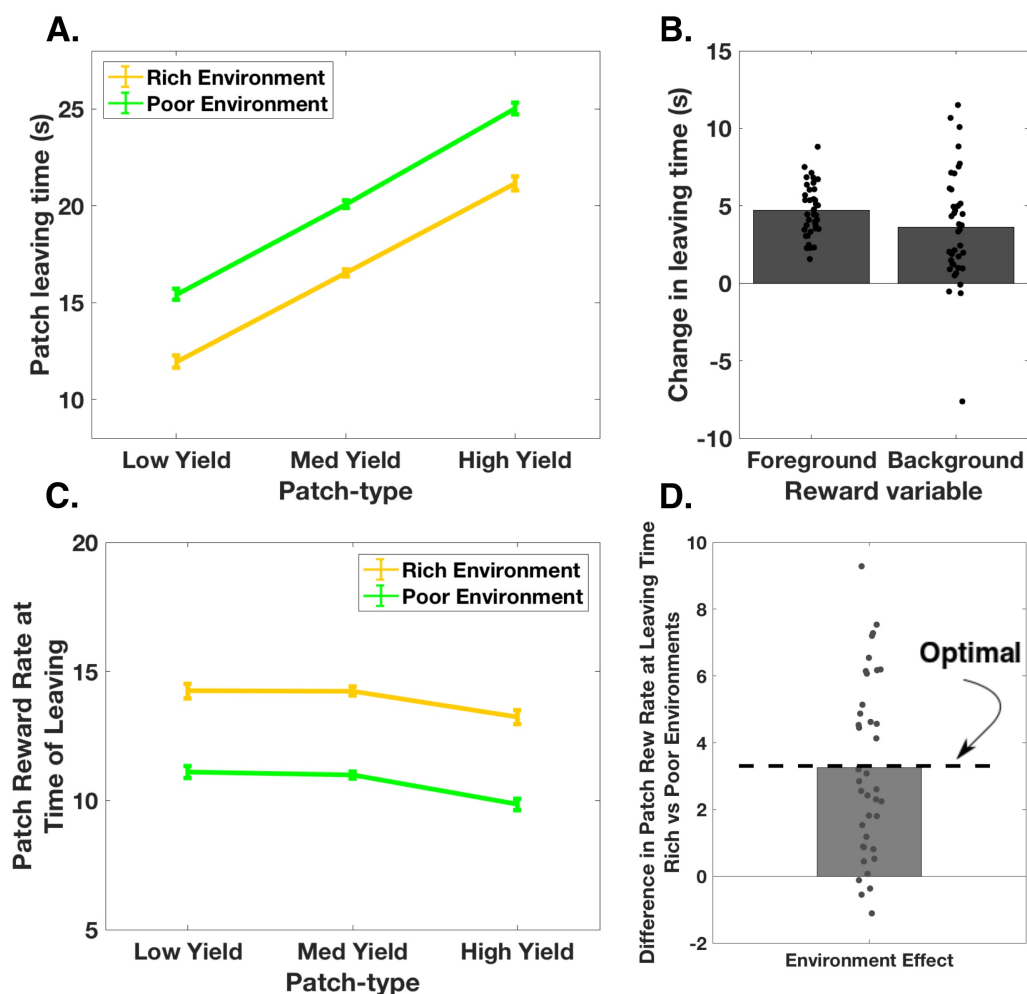
20 Within MVT the foreground and background reward rates should have independent effects  
21 on how long an individual remains in a patch. Participants should leave low yield patches  
22 sooner than high yield patches, and patches in rich environments sooner than patches in poor  
23 environments. In line with these hypotheses, we found a main effect of foreground reward, a  
24 main effect of background reward, but no interaction on participants’ (N = 39) decisions  
25 about when to leave their current patch (Foreground:  $F(1,74.6) = 528, p < 0.0001$  ;  
26 Background:  $F(1,37.5) = 40, p < 0.0001$ ; Foreground  $\times$  Background:  $F(1,1929) = 1.6, p =$   
27  $0.2$ ; **Supplementary Table 1A**). Furthermore, participants’ behaviour conformed to  
28 predicted directionality of these effects, with higher patch yield, and poor compared to rich  
29 background environment, both leading to later patch leaving times (**Figure 2A & 2B**).  
30

### 31 ***Are healthy people optimal foragers?***

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

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

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

14 (A) Participants ( $N = 39$ ) left patches later when the background environment was poor, compared to rich ( $p <$   
 15  $0.00001$ ), and when patches had higher, compared to lower yields ( $p < 0.00001$ ), with no interaction between  
 16 patch-type and background environment ( $p = 0.2$ ). (B) These effects of changing reward parameters were in the  
 17 predicted direction, with participants leaving on average 4.7s later as patch-type varied, and 3.6s later in poor



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

8  
9  
10 MVT makes two core predictions about behaviour as foreground and background reward  
11 rates change, which can be used to assess optimality of foraging behaviour (independent to  
12 any systematic bias to remain in patches longer – **Supplemental Figure 1**). Firstly, as the  
13 background environment varies (poor vs rich), the reward rate at leaving a given patch-type  
14 should differ by this same amount. Secondly, foragers should adjust their leaving time as  
15 patch quality varies, such that the instantaneous reward at leaving is the same in each patch  
16 (for a given background environment). That is within an environment, each patch should be  
17 left, regardless of its yield, when the rate at which milk is being accrued is the same.

18 Strikingly, participants varied their leaving times as background environment changed, such  
19 that the difference in reward rate between the two conditions was very close to the actual  
20 difference in background reward rates (mean difference in reward rate at leaving = 3.33,  
21 actual difference between environments if behaving optimally = 3.30,  $t_{38} = 0.07$ ,  $p = 0.95$ ,  
22 **Figure 2C & 2D**). In contrast, the foreground reward rate at patch leaving did vary across  
23 patch type (RM-ANOVA  $F(1.5,42) = 6.73$ ,  $F = 6.73$ ,  $p = 0.005$ ). Although the instantaneous  
24 reward rate on leaving low and medium yield patches did not differ (mean difference = 0.06,  
25  $t_{37} = 0.2$ ,  $p = 1$ ), participants remained in high yield patches until the instantaneous reward  
26 rate was lower compared to both medium yield (mean difference = 1.1,  $t_{37} = 3.8$ ,  $p = 0.002$ ),  
27 and low yield patches (mean difference = 1.1,  $t_{37} = 2.6$ ,  $p = 0.04$ ; **Figure 2C**).

28  
29 Thus, participants' sensitivity to changes in foraging parameters was close to optimal  
30 predictions, adjusting leaving times in response to changes in their background environment  
31 to closely match the actual changes in background reward rate. They also adjusted their  
32 leaving behaviour such that the reward rate at leaving did not differ between low and medium  
33 yield patches, although they tended to leave high yield patches later (i.e. after patch reward  
34 rate had dropped further).

35

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

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

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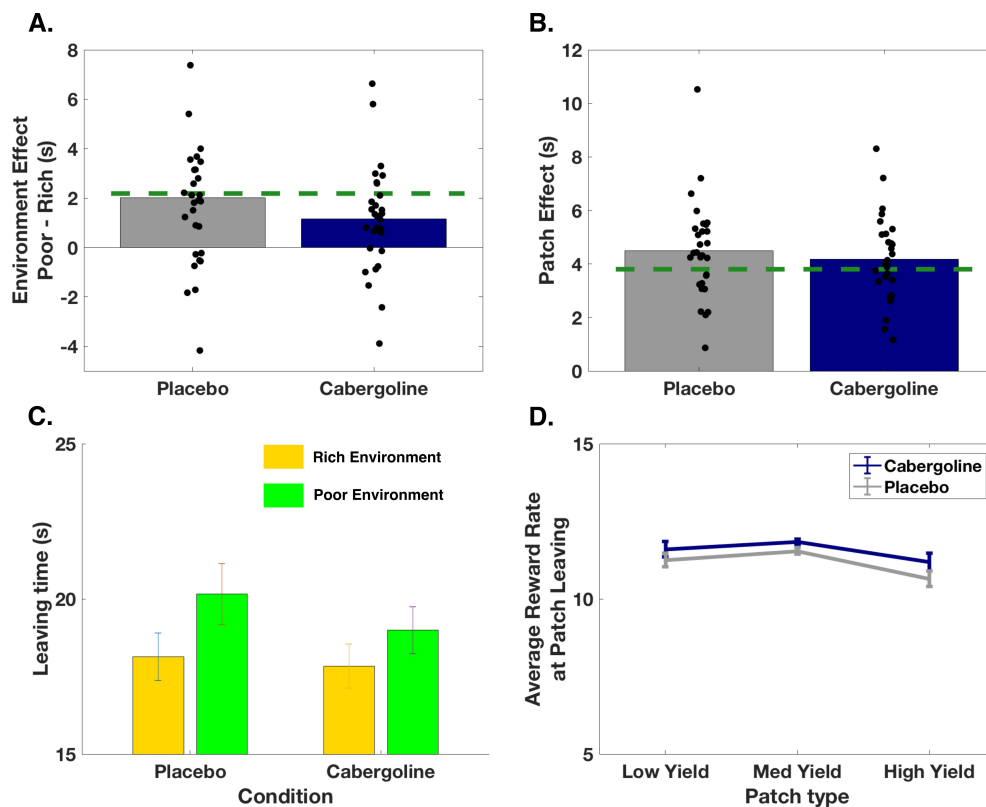
14 We hypothesised that modulating dopamine levels would not alter the effect of foreground  
15 reward rate on patch leaving, if manipulating tonic levels predominantly effects the  
16 processing of average reward rates. In line with this hypothesis, there was no significant drug  
17  $\times$  patch interaction ( $F(1,187) = 1.29$ ,  $p = 0.26$ ): cabergoline did *not* lead to a significant  
18 change in the way participants used foreground reward rate information to guide leaving  
19 decisions (**Figure 3B**). There was also no statistically significant difference in leaving times  
20 overall on drug compared to placebo (mean difference = 0.73s,  $F(1,29) = 1.86$ ,  $p = 0.18$ ), nor  
21 did the reward rate at leaving vary as a function of drug state (mean difference = 0.39,  $t_{28} =$   
22 0.8,  $p = 0.41$ ; **Figure 3D**).

23

24 The observed drug  $\times$  background reward rate interaction was present across all patch types,  
25 with no 3-way interaction ( $F(1,186) = 0.31$ ,  $p = 0.58$ ). All of these results remain after  
26 controlling for weight, height, BMI and also for any effects of learning (see **Supplemental**  
27 **material: control analyses**). Additionally, the main effects reported in study 1 were  
28 replicated in this study of elderly healthy people, with both foreground (patch) and  
29 background (environment) reward rates significantly influencing patch leaving time, and no  
30 interaction between the two (Foreground:  $F(1,57) = 425$ ,  $p < 0.0001$ ; Background:  $F(1,28) =$   
31 16.9,  $p = 0.0003$ ; Foreground  $\times$  Background:  $F(1,197) = 0.03$ ,  $p = 0.86$ ; **Figure 3A and 3B**).

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### 3 **Fig 3. Cabergoline alters use of background reward information to guide patch leaving**

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

14

15

16 Could participants be paying less attention when off medication? We analysed leaving time  
 17 variability to examine whether participants' decisions were more noisy as a function of drug  
 18 state. There was no significant difference in the variance of each participant's decisions  
 19 between placebo and cabergoline conditions (Mean Difference  $_{PLAC-CAB} = 0.31$ ,  $t_{28} = 1.34$ ,  $p =$   
 20  $0.19$  – **Supplemental Figure 3**).

21

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

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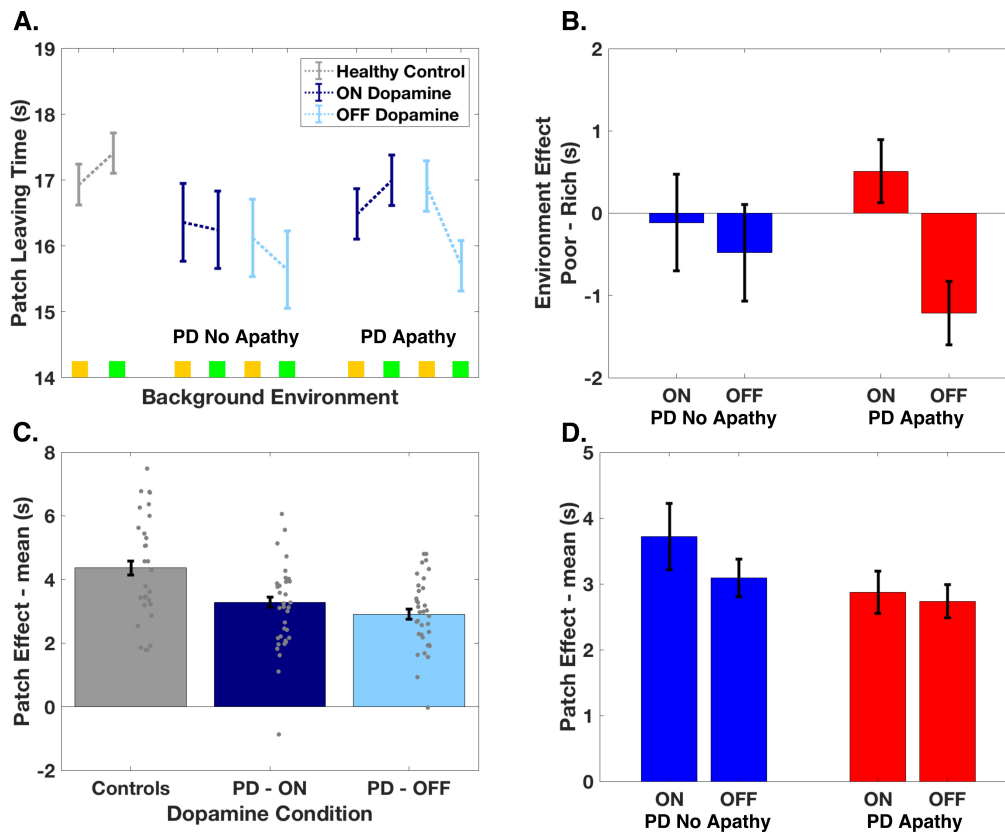
### 7 ***Dopamine and apathy influence the effect of reward context in Parkinson's disease***

8 Previous evidence implicates dysfunction of the mesolimbic dopaminergic system in PD  
9 apathy (29,30,37). We hypothesised that this observation might be underpinned by reduced  
10 dopamine levels leading apathetic patients to chronically underestimate the (background)  
11 reward environment, and therefore not switch from their current behavioural states (even if  
12 these are minimal or effectively inertial). Consistent with this prediction, we found a  
13 significant 3-way interaction between background reward rate, being ON vs OFF  
14 dopaminergic medication and whether patients were apathetic or not ( $F(1,200) = 7.03, p =$   
15  $0.009$ , **Supplementary Table 1C**). Specifically, dopamine altered the behavioural effect of  
16 the environment in patients with apathy, but not in those who were not apathetic.

17

18 In the OFF dopamine drug state apathetic PD patients showed a *reversal* of the expected  
19 effect of background environment on patch leaving time, leaving *earlier* in poor  
20 environments than in rich ones (**Figure 4A & B**). However, in the ON dopamine state their  
21 leaving decisions were not significantly different from predicted optimal behaviour, leaving  
22 patches later when background environment was *poorer* (change in environmental effect ON-  
23 OFF:  $t_{17} = 2.24, p = 0.038$ ). In contrast, changing dopamine levels did not alter the effect of  
24 environment on patch leaving time in non-aphathetic patients (change in environmental effect  
25 ON-OFF:  $t_{16} = 0.31, p = 0.76$ ). Compared to HC, the effect of environment trended towards  
26 being significantly different from the PD apathy OFF group, and was not significantly  
27 different from the PD apathy ON group or either PD non-aphathetic group; [Mean  
28 environment effect: HC = 0.5s, PD apathy ON = 0.5s, PD apathy OFF = -1.2s, PD no apathy  
29 ON = -0.1s, PD no apathy OFF = -0.5s; post-hoc unpaired t-tests: HC vs PD Ap-ON:  $t =$   
30  $0.03, p = 0.98$ ; HC vs PD Ap-OFF:  $t = 1.84, p = 0.07$ ; HC vs PD NoAp-ON:  $t = 0.54, p =$   
31  $0.59$ ; HC vs PD NoAp-OFF:  $t = 1.07, p = 0.29$ ].

32



1

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

4 (A) There was a significant interaction between background reward rate, dopamine and apathy ( $p=0.009$ ). Raw  
 5 leaving times in each environment (rich and poor – gold and green boxes respectively), collapsed across patch-  
 6 type, are shown for non-apathetic ( $N = 17$ ) and apathetic ( $N = 18$ ) PD patients, in the ON and OFF states, as  
 7 well as the healthy control group ( $N = 29$ ). There was no main effect of dopamine or apathy on leaving time. (B)  
 8 Dopamine specifically changed the influence of background reward environment on switching behaviour, but  
 9 only in the patients with apathy (ON vs OFF paired T-test, PD Apathy group:  $p = 0.038$ ; PD No Apathy group:  
 10  $p = 0.76$ ). (C & D) There was no interaction between dopamine, apathy and the influence of foreground reward  
 11 rate on patch leaving ( $p=0.58$ ). Parkinson's disease was associated with a significantly reduced effect of  
 12 foreground reward rate on leaving time, independent of dopamine condition (C – Unpaired T-test Control vs  
 13 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  
 14 OFF paired T-test, PD Apathy group:  $p = 0.6$ ; PD No Apathy group:  $p = 0.31$ ). Error bars are  $\pm$  SEM.

15

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

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

3

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

5 As in the healthy control population, foreground (patch) reward rate strongly predicted  
6 leaving times ( $F(1,68) = 252, p < 0.0001$ , **Supplementary Table 1C**). However, neither  
7 change in dopamine state or baseline motivation affected the degree this variable influenced  
8 patch leaving behaviour (patch  $\times$  DA:  $F(1,188) = 1.02, p = 0.31$ ; patch  $\times$  apathy:  $F(1,68) =$   
9  $2.26, p = 0.14$ ; **Figure 4C & D**). In contrast, the magnitude of the patch effect was reduced as  
10 a function of disease, with PD patients – whether ON or OFF their dopaminergic drugs –  
11 showing reduced sensitivity to this metric compared to HCs; [Mean patch effect: HC = 4.4s,  
12 PD-ON = 3.3s, PD-OFF = 2.9s; one-way ANOVA (group effect)  $F(2,96) = 7.41, p = 0.001$ .  
13 Post-hoc t-tests: HC vs PD-ON: MD = 1.1s,  $t = 2.48, p = 0.016$ ; HC vs PD-OFF: MD = 1.5s,  
14  $t = 4.12, p = 0.0001$ ; PD-ON vs PD-OFF: MD = 0.38s,  $t = 1.06, p = 0.29$ ].

15

#### 16 ***No general effects of motivation and dopamine on patch leaving***

17 Neither dopamine nor apathy had independent main effects on patch leaving time ( $F(1,35) =$   
18  $0.09, p = 0.77$  &  $F(1,35) = 0.12, p = 0.73$  respectively; **Supplementary Table 1C**). There  
19 was also no two-way interaction between dopamine and motivational state ( $F(1,35) = 0.003,$   
20  $p = 0.96$ ), nor were other two-way, three-way or the full four-way interactions significant.  
21 Furthermore, as with the Cabergoline study, the dopaminergic manipulation was not  
22 associated with a change in variance of patch leaving decisions ( $MD_{ON-OFF} = 0.25, t_{34} = 1.25,$   
23  $p = 0.22$ ; **Supplemental Figure 3**), nor did this metric differ with apathy status (One-way  
24 ANOVA:  $F(2,61) = 1.1, p = 0.34$ , **Supplemental Figure 3**).

25

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

31

## 1 DISCUSSION

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

11  
12 The results provide new evidence for the role of dopamine in decision-making. Specifically,  
13 manipulation of dopamine levels modulated the influence of background – but not  
14 foreground – reward rate on dynamic decisions about when to switch behaviour (**Figures 3**  
15 **and 4**). Although we do not explicitly measure firing rates of dopamine neurons, the drug  
16 manipulations used putatively alter tonic dopamine levels (36), a component of the  
17 dopaminergic neuromodulatory system which has been ascribed, in the context of motor  
18 responses, a crucial although at times controversial role in signalling background reward rates  
19 (1,19,22). Although some existing evidence suggests tonic dopamine levels encode  
20 information about background reward rate, and therefore the opportunity cost (alternatives  
21 that are foregone) of chosen actions (19,21), others have argued it encodes a more specific  
22 signal for the value of a current action, independent of environmental context (22). Here, we  
23 show that changing dopamine levels modulates the effect of background reward rates, not on  
24 actions *per se*, but rather on the more abstract decision of when to move on within an  
25 environment. Crucially, changes in dopamine tone did not alter the influence of foreground  
26 reward rate on patch leaving, nor did the variance of participants' decisions change with drug  
27 state. The results were therefore specific to a component of the context in which rewards are  
28 being accrued (background reward rate), and could not be explained by a confounder such as  
29 altered attention as a function of drug. They accord with work suggesting that mesolimbic  
30 dopamine plays a role in the trade-off between exploring and exploiting currently available  
31 instrumental rewards (38–40), a situation that can also be understood within a MVT  
32 framework (17). These findings place tonic dopamine at the core of how foraging decisions  
33 are made. Furthermore, although dopamine levels in the PD patients were mainly altered via

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

4  
5 The results presented here also reveal a precise cognitive mechanism by which dysfunction of  
6 dopaminergic systems could lead to apathy (**Figure 4**). A role for dopamine as a contextual  
7 signal of background reward rate, thus influencing ‘exploration’ behaviour, has clear appeal  
8 as a mechanistic account of apathy (27). Simply, the hallmark of apathetic behaviour –  
9 reduced goal-directed activity – may occur because of an impaired ability to estimate or  
10 utilise information about background reward rates, impeding switching behaviour from a  
11 current activity (even if this activity is very minimal). Apathy is a common and debilitating  
12 complication of many neurological and psychiatric conditions, and has been associated with  
13 disrupted reward systems across many disorders – including Parkinson’s disease  
14 (3,8,31,32,42), cerebral small vessel disease (43) and schizophrenia (44). An abundance of  
15 evidence links dopaminergic systems to the processing of rewarding outcomes, encoding the  
16 value of potential actions and motivating behaviours towards goals (1–3,7,12,18,45).  
17 However, evidence to date suggests that – in tasks where reward is treated as a single  
18 construct – dopamine exerts its influence on behaviour in a dissociable manner to apathy  
19 (8,31).

20  
21 Here, the results demonstrate a specific interaction between apathy and the effect of  
22 background reward rate on patch leaving decisions, as a function of dopaminergic tone. In the  
23 OFF state, apathetic patients showed a *reversal* of the predicted effect of background reward  
24 rate (23), persisting in patches for longer when environmental reward rates were higher. This  
25 behaviour is not consistent with patients simply estimating environmental reward rate as  
26 lower, but rather suggests a failure to utilise available information about reward context to  
27 appropriately guide decisions. Consistent with the main hypotheses of this study, dopamine  
28 restored apathetic (but not non-apathetic) patients’ behaviour to the predicted direction  
29 (leaving patches earlier in rich compared to poor environments). In contrast, neither  
30 dopamine state nor apathy altered the influence of foreground reward rate on patch leaving,  
31 which instead varied as a function of disease. Overall, this offers a new interpretation of the  
32 relationship between reward and apathy. Specifically, apathetic patients used background  
33 reward information mal-adaptively to guide decisions of when to move on, dependent on  
34 baseline dopamine levels. This result is consistent with the hypothesis that disrupted



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

5  
6 Our results also highlight that human behaviour in an ecologically-derived decision making  
7 task is closely described by a normative model based on the principles of the marginal value  
8 theorem (**Figure 2**) (14,24). This accords with earlier field work in behavioural ecology  
9 (14,23) and anthropology (46,47) literatures, and more recent work beginning to explore the  
10 neural basis of such decisions (35). In the current study, the use of a foraging framework  
11 informed by MVT enabled us to dissociate the effects of reward rates on different time  
12 scales, in a way that is not possible in reinforcement-learning based manipulations of average  
13 reward rates, where the receipt of an instrumental reward instantaneously increases average  
14 reward rate (15,19). Here, participants utilised these dissociable aspects of their reward  
15 environment to adjust patch leaving behaviour in close to an optimal fashion, as both  
16 foreground and background reward rates varied. This provides evidence for a common  
17 decision principle guiding foraging-style behaviour in both humans and other animals, and  
18 allows further investigation of the specific neural mechanisms underlying it.

19  
20 Although the effects of changing dopamine levels were specific to background reward rate  
21 across studies, a differing pattern of effect on how this information altered patch leaving  
22 decisions was observed between the cabergoline manipulation in healthy people, and  
23 dopamine medication manipulation in apathetic patients with PD. One explanation for such  
24 opposing effects is that whilst the ON state in PD patients is associated with increased  
25 dopaminergic tone (as demonstrated by reduced motor disability scores – **Table 1**), the  
26 relatively low dose of cabergoline administered to healthy participants could theoretically,  
27 via actions on pre-synaptic D2 autoreceptors, reduce tonic dopamine (48–50). An alternative  
28 possibility is suggested by past research examining the effects of dopamine on cognitive  
29 control, which has highlighted an inverted-U shaped function, characterised by detrimental  
30 effects on behaviour if tonic dopamine levels are too high or too low (51). Our results are  
31 consistent with such an inverted U-shaped function. Apathetic PD patients, in whom previous  
32 work has demonstrated reduced levels of dopamine (30,37), show a lack of ability to  
33 appropriately process average reward rates when OFF their medication, but are restored – and  
34 closer to optimal – when on their medication (**Fig 4**). However, healthy individuals show

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

6  
7 Irrespective of the exact pharmacological mechanism underlying our observations, the  
8 experiments presented here demonstrate a robust, consistent effect of dopamine on the  
9 responsiveness to background reward rate, modulated in the last study by apathy status.  
10 Importantly, variance in patch leaving times did not change as a function of dopamine or  
11 apathy state. This, along with the specific rather than general changes in behaviour we  
12 observed, make it unlikely in our opinion the observed results can be explained by a  
13 confounding factor such as reduced attention or motor disturbance in the OFF state.  
14 Furthermore, the use of a continuously changing patch gain function, rather than stepped  
15 changes as has been used in previous studies (52,53) minimised the use of simple heuristics  
16 to guide decisions while having the statistical advantage of leaving the dependent variable  
17 approximately normally distributed. The experimental design, grounded in MVT, allowed for  
18 a direct comparison of behaviour against normative predictions, predictions that have  
19 previously shown to hold in animals both freely foraging in the wild, and within controlled  
20 experimental setups (26,35,54).

21  
22 Recent theoretical accounts of decision making have called for a shift to more ecologically  
23 derived experiments to investigate the mechanisms of this fundamental neural process  
24 (14,15). The current results highlight the utility of such an approach. They demonstrate the  
25 applicability of a normative model validated in wild and experimental animal populations to  
26 human behaviour in health and disease. They link basic ecological models of animal  
27 behaviour to a mechanistic understanding of human decision making, highlighting the  
28 specific influence of dopaminergic systems as people decide when to move on as they pursue  
29 rewards in their environment. Furthermore, they demonstrate the translational potential of  
30 such ecologically derived approaches to understanding complex neuropsychiatric syndromes,  
31 here showing how pathological disruption of an underlying cognitive process is associated  
32 with the clinical consequence of apathy. Together, the results bring us closer to a mechanistic  
33 understanding of motivated behaviour in health and disease, demonstrating the utility of

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

3

#### 4 **MATERIALS AND METHODS**

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

10

#### 11 **Participants**

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

14

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

18

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

26

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

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

6  
7 Demographics of participants are presented in **Table 1**.

### 9 **Questionnaire and Baseline Cognitive Measures**

10 Apathy was assessed by standardised clinical interview with the patient, using the Lille  
11 apathy rating scale (LARS – range -36 to 36), which has previously been validated in PD  
12 (55). Patients were classified as apathetic if their LARS score was  $> -22$  (a cut-off  
13 corresponding to at least mild-moderate apathy levels). Severity of PD was assessed using the  
14 Unified PD rating scale (UPDRS) total score (56) and Hoehn and Yahr stage. The UPDRS-III  
15 (motor score) was repeated in the ON and OFF states. As a baseline cognitive screen, all  
16 subjects were administered the Addenbrooke’s cognitive examination version III (ACE-III)  
17 (57), and a digit span task to assess working memory (58), in the ON state. Depressive  
18 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 <sup>^</sup>	7/10	4/14	p=0.29 <sup>^</sup>
Apathy (LARS)	-21.4 (±4.5)	-26.7 (±4.1)	-21.1 (±6.5)	<b>P=0.0002</b>	-26.7 (± 3.7)	-15.9 (±3.3)	<b>p&lt;0.0001</b>
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)	<b>p&lt;0.0001</b>	11.3 (±7.0)	17.4 (±7.7)	<b>p=0.02</b>
Dysphoria sub-scale	n/a	(1.2±1.6)	(5.0±4.1)	<b>p&lt;0.0001</b>	(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)	<b>p=0.004</b>	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)	<b>p=0.0002</b>	16.7 (±3.1)	17.5(±4.1)	p=0.57

1 **Table 1. Demographics of participants in experiment two and three**

2 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; <sup>^</sup>chi-squared test; (all values are mean  
3 +/- standard deviation)

## 1 Patch Leaving Paradigm

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

11  
12 Foreground reward rate was determined by the patch reward function. Three patch-types  
13 were used, differing in the scaling factor of the reward function ( $S$  in equation one below),  
14 and corresponding to low (32.5), medium (45) and high (57.5) yield patches. The foreground  
15 reward rate, after  $T$  seconds in a patch, was determined by the equation:

16

$$17 \quad g'(T) = S * e^{-0.075*T} \quad (1)$$

18

19 Background reward rate was manipulated by varying the proportions of low, medium and  
20 high yield patches. Two environments were used: a rich environment in which 50% of the  
21 patches were high yield, 30% medium and 20% low yield, and a poor environment in which  
22 50% of the patches were low yield, 30% medium and 20% high. Therefore, the background  
23 reward rate was higher in the rich environment. MVT demonstrates that, to maximise reward  
24 gain, participants should leave each field when the instantaneous reward rate in the field  
25 (from **equation 1**) drops below the background average reward rate for the farm (determined  
26 by the environment type; **Supplemental figure 1**). Simply, for a given patch-type,  
27 participants should leave earlier in the rich environment compared to the poor environment  
28 (**Figure 1C**).

29

30 To improve engagement, the task was framed in a ‘real-world’ farmyard setting. Each patch  
31 was a field of cows returning milk, displayed on the monitor as a bucket that continuously  
32 filled during patch residency. The height of milk displayed in the bucket was proportional to  
33 the integral of equation (1) between time = 0 and  $T$ , and was updated with a frequency of  
34 20Hz. The rate of filling declined according to **equation 1**. Thus the rate of milk yield

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

10

## 11 **Procedure**

12 Before commencing the experiment participants were trained on the task elements via a  
13 structured explanation and practice session lasting approximately 20 minutes.

14 Comprehension of the different elements was checked verbally before commencing the main  
15 experiment, with participants asked to explain what each display item meant. Participants  
16 were not given any instructions as to what optimal behaviour would be. They were told they  
17 would spend an equal amount of time on the two farm types (gold and green) and that they  
18 would never run out of fields. Participants were seated in front of a desktop computer running  
19 Pyschtoolbox ([psychtoolbox.org](http://psychtoolbox.org)) implemented within MATLAB (MathWorks, USA).

20

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

22

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

28

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

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## 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|sub)+ (1|sub:patch)+(1|sub:env)+(1|sub:patch:env)

### *Experiment TWO:*

*Leaving Time* = 1 + patch \* env \* DA +(1|sub)+ (1|sub:DA) + (1|sub:patch)+(1|sub:env)+(1|sub:patch:env:DA)

### *Experiment THREE:*

*Leaving Time* = 1 + patch \* env \* DA \* Ap +(1|sub)+ (1|sub:DA) + (1|sub:patch)+(1|sub:env)+(1|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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## 1 AUTHOR CONTRIBUTIONS

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

## 6 DECLARATION OF INTERESTS

7 We declare no conflicts of interest.

## 10 REFERENCES

- 12 1. Hamid AA, Pettibone JR, Mabrouk OS, Hetrick VL, Schmidt R, Vander Weele CM, et  
13 al. Mesolimbic dopamine signals the value of work. *Nat Neurosci.* 2016  
14 Jan;19(1):117–26.
- 15 2. Salamone JD, Correa M. The Mysterious Motivational Functions of Mesolimbic  
16 Dopamine. *Neuron.* 2012;76(3):470–85.
- 17 3. Le Bouc R, Rigoux L, Schmidt L, Degos B, Welter M-L, Vidailhet M, et al.  
18 Computational Dissection of Dopamine Motor and Motivational Functions in Humans.  
19 *J Neurosci.* 2016 Jun 22;36(25):6623–33.
- 20 4. Haber SN, Knutson B. The Reward Circuit: Linking Primate Anatomy and Human  
21 Imaging. *Neuropsychopharmacology.* 2010 Jan 7;35(1):4–26.
- 22 5. Manohar SG, Chong TT-J, Apps MAJ, Batla A, Stamelou M, Jarman PR, et al.  
23 Reward Pays the Cost of Noise Reduction in Motor and Cognitive Control. *Curr Biol.*  
24 2015 Jun 29;25(13):1707–16.
- 25 6. Schultz W, Dickinson A. Neuronal Coding of Prediction Errors. *Annu Rev Neurosci.*  
26 2000 Mar;23(1):473–500.
- 27 7. Syed ECJ, Grima LL, Magill PJ, Bogacz R, Brown P, Walton ME. Action initiation  
28 shapes mesolimbic dopamine encoding of future rewards. *Nat Neurosci.* 2016  
29 Jan;19(1):34–6.
- 30 8. Le Heron C, Plant O, Manohar S, Ang YS, Jackson M, Lennox G, et al. Distinct  
31 effects of apathy and dopamine on effort-based decision-making in Parkinson's  
32 disease. *Brain.* 2018;141(5):1455–69.
- 33 9. Schultz W. Dopamine reward prediction-error signalling: a two-component response.  
34 *Nat Rev Neurosci.* 2016 Mar;17(3):183–95.

- 1 10. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent  
2 prediction errors underpin reward-seeking behaviour in humans. *Nature*. 2006 Aug  
3 23;442(7106):1042–5.
- 4 11. Salamone JD, Correa M, Farrar A, Mingote SM. Effort-related functions of nucleus  
5 accumbens dopamine and associated forebrain circuits. *Psychopharmacology (Berl)*.  
6 2007;191(3):461–82.
- 7 12. Howe MW, Tierney PL, Sandberg SG, Phillips PEM, Graybiel AM. Prolonged  
8 dopamine signalling in striatum signals proximity and value of distant rewards. *Nature*.  
9 2013 Aug;500(7464):575–9.
- 10 13. Mohebi A, Pettibone JR, Hamid AA, Wong J-MT, Vinson LT, Patriarchi T, et al.  
11 Dissociable dopamine dynamics for learning and motivation. *Nature*. 2019 May 22;1.  
12 14. Pearson JM, Watson KK, Platt ML. Decision making: The neuroethological turn.  
13 *Neuron*. 2014;82(5):950–65.
- 14 15. Mobbs D, Trimmer PC, Blumstein DT, Dayan P. Foraging for foundations in decision  
15 neuroscience: insights from ethology. *Nat Rev Neurosci*. 2018 Jul 11;19(7):419–27.
- 16 16. Rutledge RB, Lazzaro SC, Lau B, Myers CE, Gluck MA, Glimcher PW.  
17 Behavioral/Systems/Cognitive Dopaminergic Drugs Modulate Learning Rates and  
18 Perseveration in Parkinson’s Patients in a Dynamic Foraging Task. 2009;
- 19 17. Constantino SM, Dalrymple J, Gilbert RW, Varenese S, Rocco A Di, Daw N. A  
20 Neural Mechanism for the Opportunity Cost of Time. *bioRxiv*. 2017 Aug 8;173443.
- 21 18. Kurniawan IT, Guitart-Masip M, Dolan RJ. Dopamine and effort-based decision  
22 making. *Front Neurosci*. 2011;5(JUN):1–10.
- 23 19. Niv Y, Daw ND, Joel D, Dayan P. Tonic dopamine: opportunity costs and the control  
24 of response vigor. *Psychopharmacology (Berl)*. 2007 Apr;191(3):507–20.
- 25 20. Beierholm U, Guitart-Masip M, Economides M, Chowdhury R, Düzel E, Dolan R, et  
26 al. Dopamine Modulates Reward-Related Vigor. *Neuropsychopharmacology*. 2013 Jul  
27 18;38(8):1495–503.
- 28 21. Guitart-Masip M, Düzel E, Dolan R, Dayan P. Action versus valence in decision  
29 making. *Trends Cogn Sci*. 2014 Apr;18(4):194–202.
- 30 22. Zenon A, Devesse S, Olivier E. Dopamine Manipulation Affects Response Vigor  
31 Independently of Opportunity Cost. *J Neurosci*. 2016 Sep 14;36(37):9516–25.
- 32 23. Stephens DW, Krebs JR (John R. Foraging theory. Princeton University Press; 1986.
- 33 24. Charnov EL. Optimal foraging, the marginal value theorem. *Theor Popul Biol*. 1976  
34 Apr;9(2):129–36.

- 1 25. Stephens DW, Brown JS (Joel S, Ydenberg RC. Foraging : behavior and ecology.  
2 University of Chicago Press; 2007. 608 p.
- 3 26. Nonacs P. State dependent behavior and the Marginal Value Theorem. *Behav Ecol.*  
4 2001;12(1):71–83.
- 5 27. Le Heron C, Apps. MAJ, Husain M. The anatomy of apathy: A neurocognitive  
6 framework for amotivated behaviour. *Neuropsychologia.* 2018 Jul 8;118:54–67.
- 7 28. Le Heron C, Holroyd CB, Salamone J, Husain M. Brain mechanisms underlying  
8 apathy. *J Neurol Neurosurg Psychiatry.* 2019 Mar 1;90(3):302–12.
- 9 29. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson’s disease:  
10 loss of dopamine and noradrenaline innervation in the limbic system. *Brain.*  
11 2005;128(6).
- 12 30. Santangelo G, Vitale C, Picillo M, Cuoco S, Moccia M, Pezzella D, et al. Apathy and  
13 striatal dopamine transporter levels in de-novo, untreated Parkinson’s disease patients.  
14 *Parkinsonism Relat Disord.* 2015;21(5):489–93.
- 15 31. Muhammed K, Manohar S, Ben Yehuda M, Chong TT-J, Tofaris G, Lennox G, et al.  
16 Reward sensitivity deficits modulated by dopamine are associated with apathy in  
17 Parkinson’s disease. *Brain.* 2016 Jul 24;
- 18 32. Martinez-Horta S, Riba J, de Bobadilla RF, Pagonabarraga J, Pascual-Sedano B,  
19 Antonijoan RM, et al. Apathy in Parkinson’s Disease: Neurophysiological Evidence of  
20 Impaired Incentive Processing. *J Neurosci.* 2014 Apr 23;34(17):5918–26.
- 21 33. Thobois S, Lhommée E, Klinger H, Ardouin C, Schmitt E, Bichon A, et al.  
22 Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with  
23 piribedil. *Brain.* 2013 May;136(5):1568–77.
- 24 34. Adam R, Leff A, Sinha N, Turner C, Bays P, Draganski B, et al. Dopamine reverses  
25 reward insensitivity in apathy following globus pallidus lesions. *Cortex.*  
26 2013;49(5):1292–303.
- 27 35. Hayden BY, Pearson JM, Platt ML. Neuronal basis of sequential foraging decisions in  
28 a patchy environment. *Nat Neurosci.* 2011;14(7):933-U165.
- 29 36. Brooks DJ, Abbott RJ, Lees AJ, Martignoni E, Philcox D V, Rascol O, et al. A  
30 placebo-controlled evaluation of ropinirole, a novel D2 agonist, as sole dopaminergic  
31 therapy in Parkinson’s disease. *Clin Neuropharmacol.* 1998;21(2):101–7.
- 32 37. Thobois S, Ardouin C, Lhommee E, Klinger H, Lagrange C, Xie J, et al. Non-motor  
33 dopamine withdrawal syndrome after surgery for Parkinson’s disease: predictors and  
34 underlying mesolimbic denervation. *Brain.* 2010 Apr 1;133(4):1111–27.

- 1 38. Kayser AS, Mitchell JM, Weinstein D, Frank MJ. Dopamine, Locus of Control and the  
2 Exploration-Exploitation Tradeoff. *Neuropsychopharmacology*. 2015 Jan  
3 30;40(2):454–62.
- 4 39. Daw ND, O’Doherty JP, Dayan P, Seymour B, Dolan RJ. Cortical substrates for  
5 exploratory decisions in humans. *Nature*. 2006 Jun 15;441(7095):876–9.
- 6 40. Westbrook A, Frank M. Dopamine and proximity in motivation and cognitive control.  
7 *Curr Opin Behav Sci*. 2018 Aug 1;22:28–34.
- 8 41. Beaulieu J-M, Gainetdinov RR. *The Physiology, Signaling, and Pharmacology of*  
9 *Dopamine Receptors*. 2011;
- 10 42. Lawrence AD, Goerendt IK, Brooks DJ. Apathy blunts neural response to money in  
11 Parkinson’s disease. *Soc Neurosci*. 2011 Oct;6(5–6):653–62.
- 12 43. Le Heron C, Manohar S, Plant O, Muhammed K, Griffanti L, Nemeth A, et al.  
13 Dysfunctional effort-based decision-making underlies apathy in genetic cerebral small  
14 vessel disease. *Brain*. 2018;141(11):3193–210.
- 15 44. Strauss GP, Waltz JA, Gold JM. A Review of Reward Processing and Motivational  
16 Impairment in Schizophrenia. *Schizophr Bull*. 2014 Mar 1;40(Suppl 2):S107–16.
- 17 45. Schultz W. Behavioral dopamine signals. *Trends Neurosci*. 2007;30(5):203–10.
- 18 46. Smith EA, Bettinger RL, Bishop CA, Blundell V, Cashdan E, Casimir MJ, et al.  
19 Anthropological Applications of Optimal Foraging Theory: A Critical Review [and  
20 Comments and Reply]. *Curr Anthropol*. 1983 Dec 19;24(5):625–51.
- 21 47. Metcalfe D, Barlow KR. A Model for Exploring the Optimal Trade-off between Field  
22 Processing and Transport. Vol. 94, *American Anthropologist*. Wiley American  
23 Anthropological Association; 1992. p. 340–56.
- 24 48. Chen Y-CI, Choi J-K, Andersen SL, Rosen BR, Jenkins BG. Mapping dopamine  
25 D2/D3 receptor function using pharmacological magnetic resonance imaging.  
26 *Psychopharmacology (Berl)*. 2005 Aug 5;180(4):705–15.
- 27 49. Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine  
28 system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience*.  
29 1991;41(1):1–24.
- 30 50. Pizzagalli DA, Evins AE, Schetter EC, Frank MJ, Pajtas PE, Santesso DL, et al. Single  
31 Dose of a Dopamine Agonist Impairs Reinforcement Learning in Humans: Behavioral  
32 Evidence from a Laboratory- based Measure of Reward Responsiveness NIH Public  
33 Access. *Psychopharmacol*. 2008;196(2):221–32.
- 34 51. Cools R, D’Esposito M. Inverted-U-Shaped Dopamine Actions on Human Working

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

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