

# A Trade-Off between Feedback-Based Learning and Episodic Memory for Feedback Events: Evidence from Parkinson's Disease

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## Key Words

Delayed feedback · Dopaminergic medication · Episodic memory · Feedback-based learning · Hippocampus · Incremental learning · Memory function · Striatum

## Abstract

Parkinson's disease (PD) is characterized by a loss of dopaminergic projections to the striatum, leading to both motor and cognitive impairments. The cognitive impairments are relatively selective and include deficits in incremental learning from trial-by-trial feedback, while other forms of learning, such as hippocampal-dependent episodic memory, remain intact. Interestingly, it has been suggested that the striatum and the hippocampus compete during learning, leading to the intriguing prediction that the striatal disruption in PD could lead to enhanced performance on tasks that depend on the hippocampus. We tested this prediction by simultaneously assessing incremental learning and episodic memory for trial-unique feedback events, within a single task, in patients with PD. Further, in order to modulate the engagement of the striatum versus the hippocampus, we manipulated the timing of feedback during learning, building on prior results showing that delaying feedback by a few seconds shifts learning to depend on the hippocampus instead of the striatum. We found that Parkinson's patients were impaired at learning from immediate feedback, but had enhanced episodic memory for those immediate feed-

back events. Thus, our results provide evidence for concurrent impaired and enhanced learning and memory functions within the same group of patients from a single task.

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## Introduction

Parkinson's disease (PD) is characterized by severe loss of nigrostriatal dopaminergic neurons [1, 2] and is well known to impair motor function. More recently, it has been recognized that cognitive functions are impacted as well [3–10]. Understanding the precise nature of these cognitive symptoms and how they are affected by treatment for PD is of tremendous interest to both basic and clinical research.

Characterization of the cognitive symptoms in PD has benefited greatly from recent advances in system neuroscience that have elucidated the critical role of the striatum and its dopaminergic inputs in learning to predict rewards and acting to obtain them [11–13]. Indeed, PD leads to impairments in feedback-driven learning [14–20, for review, see 21–23]. Importantly, these learning impairments and other cognitive symptoms are modulated by the dopaminergic replacement therapy used to treat PD [15, 24–29], and consistent with theories and models regarding the role of striatal dopamine in reward-based learning [11, 12, 30, 31], the effect of dopaminergic medication differs as a

function of valence (i.e. whether behavior is driven by reward or by punishment) [15, 25, 32]. In addition, more recent findings indicate that dopamine has separable effects on the acquisition versus the performance of learned associations [33, 34]. Thus, although significant advances have been made, the precise mechanisms contributing to deficits in PD still require further understanding.

Interestingly, feedback-based learning impairments in PD appear to be as selective as they are ubiquitous, that is, other forms of learning are generally spared. In particular, a wealth of research has provided evidence for a dissociation between the roles of the striatum and the hippocampus in learning [4, 16, 35]. This idea is based partly on studies that contrasted learning and memory in PD patients versus amnesics with damage to the hippocampus [4]. Such studies have demonstrated that the striatum supports incremental learning of actions or responses, often referred to as ‘procedural’ learning, whereas the hippocampus supports rapid formation of explicit memories for episodes, often referred to as ‘episodic’ memory [36, 37]. For example, amnesics show intact performance on simple feedback-based learning tasks but demonstrate virtually no episodic memory for events that took place during the experiment [38, 39]. By contrast, PD patients have intact episodic memories but marked difficulties in simple feedback-based learning [4]. The idea that multiple memory systems can support behavior offers the tantalizing promise that if learning of information could be shifted to depend less on the striatum and more on the hippocampus, then the learning impairments in PD could be remediated.

Furthermore, it has been suggested that the striatum and the hippocampus compete for behavioral control [3, 40, 41]. Studies using functional magnetic resonance imaging (fMRI) with healthy participants have shown negative correlations between blood oxygenation level-dependent (BOLD) activity in the striatum and the hippocampus during learning, which has been suggested to reflect competition between these memory systems [42–44]. Consistent with such results, greater BOLD activity in the hippocampus of mildly affected PD patients compared with healthy controls has been shown during intact feedback-based learning [45]. In addition, studies in rodents have reported that damage to one system enhances learning in the other [3, 40, 46–54]. If so, then patients with PD may actually be *better* than healthy individuals at episodic learning. So far, however, no evidence for this has been reported in humans.

We reasoned that the lack of evidence in favor of enhanced episodic function in patients with PD could be

due to the very different ways in which episodic and procedural memory have been measured in past studies. For example, episodic memory assessment in feedback-based learning tasks has consisted of multiple-choice questions about global task features, as opposed to assessing memory for trial-unique events related to the information being learned, such as memory for the feedback event itself [4, 35, 39]. An additional challenge in understanding the trade-off between incremental and episodic learning systems is that despite existing evidence for dissociations between each system, there has not been a good understanding of the variables that modulate the systems. That is, there has been a lack of reliable ways to experimentally shift learning from recruiting the striatum to recruiting the hippocampus within a single task.

We recently found that one way to shift learning from the striatum to the hippocampus is by delaying the feedback on each trial by just a few seconds [18]. Using fMRI in healthy people, we observed that the striatum supported incremental learning of stimulus-outcome associations when the trial-by-trial feedback arrived immediately (within 1 s) after a response. However, when the same information was learned under conditions of delayed feedback (7 s after a response), learning was supported by the hippocampus. In PD patients, we found impaired learning from immediate feedback but spared learning from delayed feedback. Thus, a subtle manipulation of the timing of feedback pushed learning to be supported by the hippocampus instead of the striatum, remediating learning impairments in PD [18].

In the present study, we asked: (1) Does learning from immediate versus delayed feedback impact episodic memory for feedback in PD? (2) Does dopaminergic medication affect learning from immediate versus delayed feedback?

To address these questions, we compared learning from immediate versus delayed feedback in PD patients ‘on’ or ‘off’ dopaminergic medication. Importantly, we presented all participants with feedback events in the form of trial-unique images, allowing us to assess both incremental learning and episodic memory for trial-unique feedback events in a single task.

## Participants and Methods

### *Participants*

Thirty-four participants with a diagnosis of idiopathic PD were recruited from the Center for Parkinson’s Disease and Other Movement Disorders at the Columbia University Medical Center Department of Neurology with the assistance of Dr. Lucien

**Table 1.** Demographic characteristics of the participants

	AC (n = 25)	PD-on (n = 12)	PD-off (n = 14)
Age, years	65.7 ± 8.1	63.1 ± 6.6	67.2 ± 7.7
Education, years	16.2 ± 1.5	16.1 ± 2.0	16.7 ± 3.5
MMSE	29.5 ± 0.6	29.4 ± 0.8	29.6 ± 0.6
COWAT	45.4 ± 12.2	46.2 ± 10.3	42.9 ± 13.8
NAART	15.9 ± 8.3	16.9 ± 5.2	17.4 ± 8.9
Digit span	12.3 ± 2.1	12.2 ± 1.6	11.4 ± 1.6
Beck depression inventory <sup>1</sup>	3 ± 2.0	4.3 ± 1.8	8.6 ± 6.4
Cognitive	0.8 ± 1.2	0.6 ± 0.8	2.0 ± 1.7
PD onset		10.0 ± 6.4	4.1 ± 4.1
UPDRS			
Total 'on' <sup>2</sup>		32.9 ± 14.9	27.9 ± 13.2
(I) Mentation, behavior, mood		0.7 ± 0.9	0.4 ± 0.7
(II) Activities of daily living <sup>3</sup>		9.9 ± 4.2	6.0 ± 3.8
(III) Motor examination		22.3 ± 11.7	21.5 ± 10
Hoehn-Yahr scale		1–3	1–3

Values are means ± SD. Unless noted, groups did not differ in any measures ( $p > 0.5$ ). AC = Age-matched, healthy controls; UPDRS = Unified Parkinson's Disease Rating Scale; COWAT = Control Oral Word Association Test; NAART = North American Adult Reading Test; MMSE = Mini Mental Status Examination.

<sup>1</sup> Controls differed significantly from the PD patients overall (PD-on + PD-off patients),  $p = 0.024$ .

<sup>2</sup> UPDRS scores were assessed while patients were on dopaminergic medication.

<sup>3</sup> PD-on and PD-off patients differed significantly in their UPDRS II scores ( $p = 0.028$ ).

Cote and through Fox Trial Finder and PDtrials, online databases for volunteers interested in participating in research on PD. Only patients in mild or moderate disease stages (Hoehn and Yahr stages 1–3) were recruited.

Controls were recruited from the community surrounding Columbia University and matched on age and education. All participants provided informed consent in accordance with the guidelines of the Institutional Review Board of Columbia University and were paid USD 12/h for their participation. Participants were excluded if they had suffered brain injury or were diagnosed with neurological or psychiatric disorders other than PD.

All participants completed a battery of neuropsychological tests and were excluded if they exhibited any general cognitive impairment (scoring 27 or below on the Mini-Mental State Examination) or signs of depression (scoring 7 or above – more than 2 SDs above the mean – on the cognitive subscale of the Beck Depression Inventory). The remaining 26 PD patients and 25 control participants did not differ in age, education, or measures of IQ and frontal executive functions (all  $p > 0.25$ ; table 1).

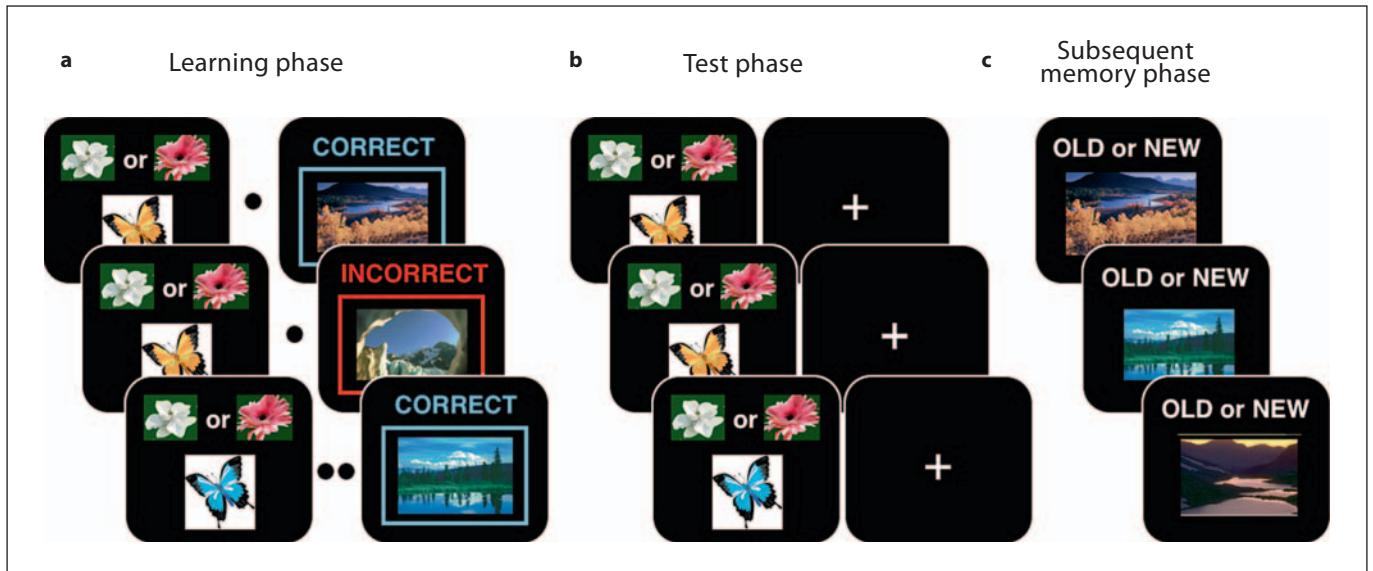
We tested patients while either 'on' or 'off' their medications. Patients 'on' medication ( $n = 12$ ) were tested within 3 h of their last medication dose. Patients 'off' medication ( $n = 14$ ) were withdrawn from medications taken for PD overnight and tested at least 16 h after their last medication dose. Five participants in the 'off' group were not yet receiving dopamine replacement therapy. Of the 21 patients receiving medication (12 in the 'on' group, 9 in the 'off' group), 8 were receiving only L-DOPA, 2 were receiving only dopamine agonists, 9 were receiving both L-DOPA and agonists, and 2 were on other medications (Azilect).

Patient groups 'on' versus 'off' medication did differ significantly on disease duration [ $t(24) = -2.83$ ,  $p = 0.009$ ] due to the inclusion of newly diagnosed patients. Without these de novo patients, disease duration did not differ significantly [ $t(19) = -1.61$ ,  $p = 0.12$ ]. Regardless, disease duration was unrelated to performance on the learning task or measures of episodic memory ( $p > 0.1$ ).

#### Task

Participants completed a probabilistic learning task that is similar to tasks previously shown to be sensitive to striatal function in humans [4, 14, 18, 35, 42]. In this type of task, participants learn to associate cues with outcomes through trial and error. Because there is no one-to-one mapping between cues and outcomes, optimal learning involves the use of response-contingent feedback across multiple trials to incrementally learn the most probable outcome.

Here, we manipulated the timing with which feedback was delivered during probabilistic learning [18]. Participants saw a cue (1 of 4 different butterflies) on each trial and had to predict which of two outcomes (different-colored flowers) that cue was associated with. Each butterfly was associated with one flower on 83% of trials and with the other flower on 17% of trials (table 2). For each cue, response-contingent feedback was presented after a fixed delay of either 1 s (immediate condition) or 7 s (delayed condition), such that two butterflies were associated with each feedback timing condition (table 2). The assignment of cues to outcomes and conditions was counterbalanced across participants. Immediate and delayed feedback trial types were interleaved throughout training.



**Fig. 1.** Task schematic. **a** In the learning phase, participants used trial-by-trial feedback to learn which flower 4 different butterflies preferred. For one set of butterflies, feedback was presented immediately. For another set of butterflies, feedback was presented with a delay. **b** After learning, participants completed a test phase

where they continued to make predictions about the butterflies' preferences. However, they no longer received feedback and the timing of all trial events was equal across trial types. **c** Participant's episodic memory for feedback events was tested in a surprise subsequent memory phase.

**Table 2.** Task structure

Stimulus	Association with outcome		Time between response and feedback <sup>1</sup> delay in seconds
	flower 1	flower 2	
<i>Butterfly</i> <sup>2</sup>			
1	83%	17%	1
2	17%	83%	1
3	83%	17%	7
4	17%	83%	7

<sup>1</sup> After a response was made, the participant was shown his or her choice for 1 s in all conditions. The delay time shown includes the 1-second choice display + 0- or 6-second delay time.

<sup>2</sup> Butterflies were counterbalanced with respect to feedback timing condition across participants. For each individual participant, the mapping between cues and delays was fixed. Associations between butterflies and flowers were also counterbalanced across participants.

Feedback events consisted of a verbal response ('correct' or 'incorrect') along with an image of an outdoor scene in a colored frame (blue for correct and red for incorrect; fig. 1a), presented on the screen for 2 s. The outdoor scenes were trial unique in order to allow us to test later episodic memory for these feedback events.

A 7-second response deadline was imposed and a reminder to respond appeared after 4 s. Participants' choices were shown immediately after responding for 1 s followed by the delay period (0 vs. 6 s) during which the chosen flower and the butterfly remained on the screen in order to minimize working memory demands (table 2).

Participants completed a short practice to ensure that they understood the task and were able to respond in the allotted time. Next they completed 96 learning trials of the task (learning phase), followed by a test phase where participants saw the butterflies from the learning phase and were told to continue performing based on what they had learned. The test phase structure resembled the learning phase, with the exception that no feedback was given and the timing of all trial parts was equivalent across trial types (fig. 1b).

A surprise recognition memory test for the feedback images (outdoor scenes) seen during the learning phase was administered 60–90 min after completing the probabilistic learning task (an unrelated task was completed in the interval). All images shown during learning (targets) and an equal number of new images (foils) were tested. On each trial, a single image was presented and participants were instructed to determine whether the image was seen during learning (old) or not seen (new; fig. 1c). They were then required to indicate their level of confidence in their choice with 1 = certain, 2 = sure, 3 = pretty sure, and 4 = guessing. Some participants did not complete the recognition memory test, leaving 22 controls and 17 PD patients for analyses of subsequent memory.

#### Data Analyses

*Probabilistic Learning.* Performance on the probabilistic learning task was assessed in terms of making optimal choices

(the degree to which participants selected the most likely outcome for each cue), as in previous studies [4, 14, 35, 38, 42, 55, 56]. The effects of feedback timing were tested in repeated-measure ANOVA.

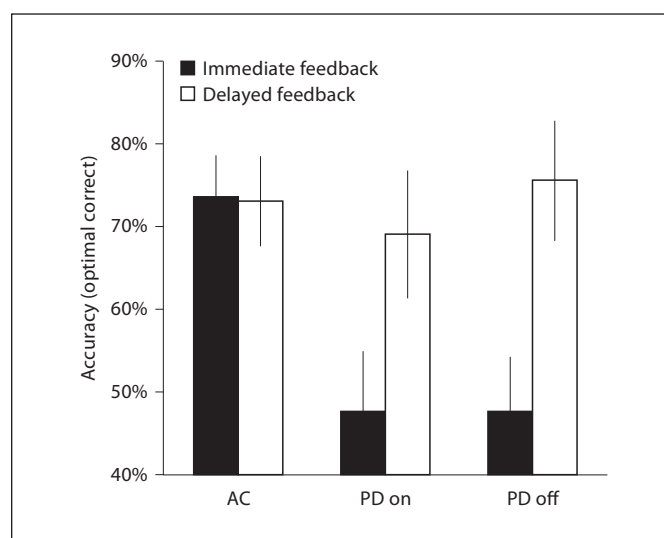
*Episodic Memory for Feedback Events.* In order to determine whether later recognition memory for feedback events differed as a function of feedback timing (immediate vs. delayed), we calculated the proportion of hits (recognizing previously seen images of outdoor scenes) and false alarms (incorrectly identifying a new image as previously seen) that had been associated with each feedback timing condition during learning. Performance was further binned according to confidence ratings, and responses labeled as guesses were excluded from subsequent memory analyses. Planned t-tests were used to compare performance between groups in each feedback timing condition.

## Results

### Probabilistic Learning

We assessed the percentage of optimal responses made during the test phase, which probed learned responses while timing was equal for all trial types and no feedback was given. First, we compared performance of all PD patients, both 'on' and 'off' dopaminergic medication, with age-matched controls in the immediate versus delayed feedback conditions. As previously reported in a smaller sample [18], we found a significant interaction between feedback timing and group [ $F(1,49) = 6.24, p = 0.016$ ; partial  $\eta^2 = 0.11$ ] as well as main effects of both feedback timing [ $F(1,49) = 56.78, p = 0.02$ ; partial  $\eta^2 = 0.11$ ] and group [ $F(1,49) = 6.99, p = 0.011$ ; partial  $\eta^2 = 0.13$ ]. Critically, as shown in figure 2, the interaction was driven by a selective impairment in the immediate feedback learning condition in PD patients [immediate:  $t(49) = -3.77, p < 0.001$ , and delay:  $t(49) = -0.65, p = 0.95$ ].

Next we assessed the effect of dopaminergic medication on learning from immediate and delayed feedback. As seen in figure 2, there was no effect of medication status on the selective impairment in learning from immediate feedback: immediate:  $t(24) < 0.01, p = 1$ , and delay:  $t(24) = 0.69, p = 0.49$ . Furthermore, numerically the selective deficit was present even among the smaller subset of 5 patients who were not yet medicated (de novo:  $M_{\text{immediate}} = 46.7\%$  correct,  $M_{\text{delay}} = 76.7\%$  correct; PD off:  $M_{\text{immediate}} = 48.1\%$  correct,  $M_{\text{delay}} = 75.0\%$  correct). Within the group of PD patients who were withdrawn from dopaminergic medication, 3 were currently taking antidepressants (with assumed serotonergic or adrenergic effects) and these participants also exhibited selective impairment in learning from immediate feedback ( $M_{\text{immediate}} = 47.2\%$  correct,  $M_{\text{delay}} = 94.4\%$  correct). Thus,



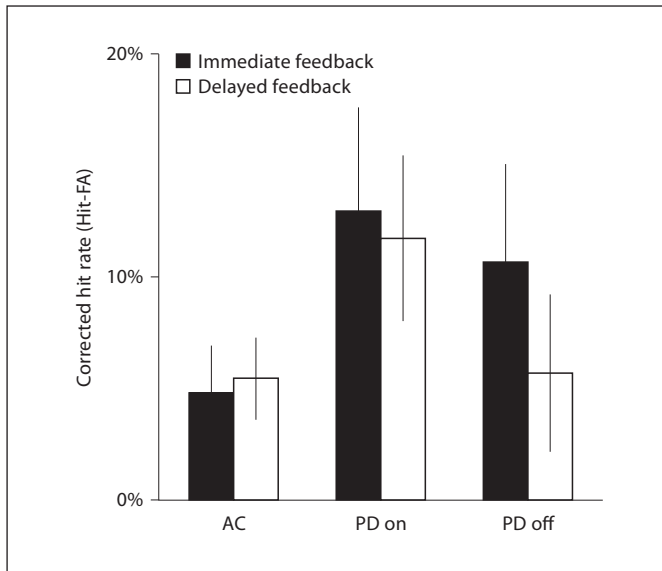
**Fig. 2.** Test phase performance for immediate versus delayed feedback in healthy, age-matched controls (AC) and PD patients 'on' and 'off' dopaminergic medication. Error bars represent  $\pm 1$  SEM.

regardless of medication status, PD patients exhibited a pattern of selective learning impairment when feedback was immediate, an impairment that was remediated in all groups when feedback was delayed by just 7 s.

We also investigated whether there were any associations between measures of cognitive function or disease severity and the impairment in learning from immediate feedback for PD patients, but there were no correlations with any measures (all  $p > 0.05$ ).

### Episodic Memory for Feedback Events

In order to assess the contribution of hippocampal-dependent episodic memory, we examined memory for feedback events that had been experienced during learning. First, we examined memory for scenes accompanying immediate feedback, the condition wherein PD patients were selectively impaired at probabilistic learning. We found that PD patients' memory for immediate feedback events was significantly *better* than that of controls [ $t(37) = 2.16, p = 0.038$ ; fig. 3]. Scene memory did not differ between the patients and controls in the delayed feedback condition [ $t(37) = 1.15, p = 0.26$ ]. Thus, whereas patients were significantly impaired at probabilistic learning from immediate feedback, they exhibited significantly better episodic memory for that feedback. In contrast, controls learned well from immediate feedback but had poorer memory for immediate feedback events than did PD patients.



**Fig. 3.** Subsequent memory performance for immediate vs. delayed feedback in healthy, age-matched controls (AC) and PD patients ‘on’ and ‘off’ dopaminergic medication. Corrected hit rates (hits minus false alarms) are shown. Responses labeled as guesses are excluded. Error bars represent  $\pm 1$  SEM.

Finally, we assessed whether dopaminergic medication affected episodic memory for immediate versus delayed feedback events. We found no significant difference in episodic memory between patients ‘on’ and ‘off’ dopaminergic medication for either immediate or delayed feedback events (all  $p > 0.2$ ).

## Discussion

Taken together, our results provide evidence for concurrent impaired and enhanced learning and memory functions within the same group of patients from a single task. Consistent with recent findings from fMRI and PD patients regarding the effect of feedback timing on striatal versus hippocampal learning [18], learning from immediate feedback was impaired in PD, whereas learning from delayed feedback was intact. Here, we extend this prior finding by showing that this pattern was present regardless of the medication status of patients.

Moreover, here we report the novel discovery that PD may incur benefits for episodic memory; patients had better episodic memory for trial-unique images that were part of the error-correcting feedback event. In particular, subsequent memory was better for images accompanying

immediate feedback. Enhanced subsequent memory for immediate feedback in PD patients, who were impaired at learning from immediate feedback, is consistent with the idea that there may be a competition between brain systems that support incremental feedback-driven learning versus long-term episodic memory [3, 40]. To the best of our knowledge, this pattern of results provides the first behavioral evidence for such competition in PD.

### *Feedback Timing Modulates Engagement of Memory Systems*

The impairment in learning from immediate feedback in PD is consistent with electrophysiological data demonstrating that dopaminergic neurons are sensitive to the interval between stimuli and outcomes. As rewards are delayed several seconds, the response of dopaminergic neurons becomes increasingly similar to the response observed to unpredicted outcomes [57, 58]. This suggests that the mechanism underlying learning becomes less effective as feedback is delayed. Yet, learning from delayed feedback is a common occurrence, which suggests that other neural systems may be engaged in support of such learning. Indeed, the finding that the hippocampus is engaged specifically when feedback was delayed [18] is consistent with the idea that the hippocampus is particularly well suited to support learning that requires bridging across space or time [59–62]. We also reported that performance in PD patients was intact when feedback was delayed, thereby demonstrating that the striatum was critical only for learning from immediate feedback. Here, we confirm this result in patients both ‘on’ and ‘off’ dopaminergic medication.

### *Enhanced Memory for Feedback Events in PD*

In addition to the impaired learning from immediate feedback and intact learning from delayed feedback, we also noted enhanced memory performance in PD patients. In particular, patients had significantly better memory for images they had seen together with feedback that was given immediately. It is notable that patients performed better than controls and that this enhanced performance was most pronounced in the feedback condition where learning was severely impaired. These results are consistent with the proposal that distinct memory systems centered in the striatum and the hippocampus interact in some manner. It has been proposed based on behavioral studies in animals and fMRI studies in humans that there is a competitive relationship between these systems [40]. That is, the normal operation of these systems is antagonistic, such that if one system is en-

gaged in learning, the other system is less likely to be engaged.

Behavioral evidence for this comes from lesion studies in rodents, where lesions to one system result in better performance on tasks that rely on the other system [3, 46, 54]. Competition has been demonstrated at the neural level in humans [42–44], but strong behavioral evidence for a trade-off in the engagement of memory systems in humans has been lacking, in particular for benefits to declarative memory following interference with procedural memory, although there have been reports of enhanced procedural learning subsequent to interference with declarative/explicit memory [41, 63, 64]. An alternative possibility to competition is that PD patients engaged neural mechanisms depending on the hippocampus, but that this effort was insufficient to support learning from immediate feedback, and instead resulted in ‘collateral’ enhancement of episodic memory for the feedback events. Either way, the results point to intriguing interplay and flexibility as memory systems are engaged in support of learning, as well as to limitations to this flexibility in how distinct memory systems can be deployed [35].

Distinguishing between possible explanations for apparent ‘competition’ between memory systems will require further data and a better understanding of the mechanisms that could plausibly mediate interactions between memory systems, be they competitive or cooperative. In the current study, enhanced memory for feedback events was unaffected by the dopaminergic status of PD patients. However, further studies are necessary to understand the effects of dopaminergic versus striatal dysfunction on the hippocampus. Studies in patients with Huntington’s disease or with focal striatal lesions would be informative in this regard. A precise functional account of the putative interaction between striatal and hippocampal memory systems is lacking, and greater clarity on these issues would present a major advance in our understanding of memory systems.

The current subsequent memory results should be viewed with caution due to the relative weakness of the effect and also due to the low overall memory performance in this task. In future work, it will be important to replicate these effects with an easier episodic memory test in order to allow for better memory performance in healthy control participants.

It should be noted that several studies have investigated declarative memory in PD in isolation, that is, without a concurrent learning component. In some cases, impairments have been observed, but currently it seems unclear whether deficits are linked to hippocampal dys-

function or deficits in strategic and executive processes that characterize some PD patients [65–70]. In addition, some studies have documented hippocampal atrophy in PD patients and linked such atrophy to declarative memory impairments [71], whereas others have found that medial temporal lobe atrophy did not differ between nondemented PD patients and healthy controls [72]. These findings point to a need for a better characterization of the structural and functional changes beyond the striatum and prefrontal cortex that accompany PD, in addition to better characterization of the learning and memory impairments in PD.

#### *Dopamine Effects on Probabilistic Learning*

In light of recent findings suggesting that some cognitive learning deficits in PD are caused by dopaminergic medication and that withdrawal from medication normalizes performance, it is surprising that there were no effects of medication status on the feedback-driven learning task [33, 34]. Perhaps, the task used here was particularly sensitive to striatal dysfunction present even in early PD. Notably, medication effects on feedback-based learning have been shown to interact with feedback valence [15, 20, 24, 25, 28, 73]. Patients ‘on’ medication (high dopamine state) learn better from positive feedback, but not from negative feedback, and the reverse is found in patients ‘off’ medication (low dopamine state). In the incremental learning task used here, learning from positive versus negative feedback cannot be effectively separated, such that we were unable to assess such effects. However, it seems unlikely that a selective inability to learn from positive feedback should result in such a severe impairment in the ‘off’ group.

#### **Conclusions**

Our findings demonstrate that multiple neural systems support feedback-driven learning and that neural systems supporting distinct learning and memory functions appear to function in an interdependent fashion rather than in isolation. Remarkably, small changes in the timing of feedback can change PD patients’ ability to learn the same information and PD patients performed better than controls when asked to remember specific episodic information about the feedback events. This pattern of results was predicted based on a cognitive neuroscience understanding of how the striatum and hippocampus contribute to learning and memory function and would be unlikely to arise solely through the study of PD.

Thus, theoretical, computational, and empirical contributions across animal and human work can be translated to clinically relevant studies by informing predictions about how to remediate deficits in PD and other neurological diseases.

## Disclosure Statement

The authors have no financial interests to disclose.

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