Research report

The role of dopamine in cognitive sequence learning: evidence from Parkinson's disease

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Abstract

Electrophysiological and computational studies suggest that nigro-striatal dopamine may play an important role in learning about sequences of environmentally important stimuli, particularly when this learning is based upon step-by-step associations between stimuli, such as in second-order conditioning. If so, one would predict that disruption of the midbrain dopamine system — such as occurs in Parkinson's disease — may lead to deficits on tasks that rely upon such learning processes. This hypothesis was tested using a "chaining" task, in which each additional link in a sequence of stimuli leading to reward is trained step-by-step, until a full sequence is learned. We further examined how medication (L-dopa) affects this type of learning. As predicted, we found that Parkinson's patients tested 'off' L-dopa performed as well as controls during the first phase of this task, when required to learn a simple stimulus–response association, but were impaired at learning the full sequence of stimuli. In contrast, we found that Parkinson's patients tested 'on' L-dopa performed better than those tested 'off', and no worse than controls, on all phases of the task. These findings suggest that the loss of dopamine that occurs in Parkinson's disease can lead to specific learning impairments that are predicted by electrophysiological and computational studies, and that enhancing dopamine levels with L-dopa alleviates this deficit. This last result raises questions regarding the mechanisms by which midbrain dopamine modulates learning in Parkinson's disease, and how L-dopa affects these processes.
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1. Introduction

In Parkinson's disease (PD), patients suffer from a severe loss of dopamine in the substantia nigra pars compacta (SNc), leading to disrupted basal ganglia function and to a loss of motor control [1]. Recent evidence suggests that PD is also associated with learning and memory deficits, implicating the basal ganglia and the midbrain dopamine system in specific aspects of learning and memory function [40,33,24].

The learning and memory deficits in PD are generally characterized as deficits in *procedural* or *habit* learning [6,39,24,13]. For example, patients with PD are impaired on visuomotor sequence learning [35,21], verbal serial reaction [52], conditional association tasks [14,54,27], and probabilistic classification learning [24] — all tasks which are thought to rely upon procedural learning. However, a precise understanding of the learning and memory deficits in PD remains elusive. In addition, there is currently no clear understanding of how the procedural deficits in PD relate to the underlying neuropathology of the disease.

Some insight into the neural bases of learning and memory deficits in PD may come from examining response patterns of SNc dopamine neurons during learning. A series of

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electrophysiological recording studies in animals suggests a role for these neurons in reward-related learning (for review see [41,42]). These studies demonstrate that midbrain dopamine neurons respond to reward-related stimuli in a temporally-specific, stimulus-specific manner during learning. Specifically, SNc dopamine neurons respond with strong phasic activity to unexpected rewards, and to cues that reliably predict reward [25]. When an expected reward fails to occur, a decrease in dopamine firing is observed [19]. It has been suggested that these characteristics of the midbrain dopamine response make it a good candidate for a learning algorithm that codes for reward prediction [43,50].

Computational modeling has suggested that midbrain dopamine may code for a temporal-difference algorithm, which is particularly important for phenomena such as second-order conditioning, or learning that is based on 'chaining' sequences of events leading to reward [43,46]. The key feature of these paradigms is that the organism is able to learn to associate between stimuli and rewards that are not contiguous with the stimuli. For example, as mentioned, SNc dopamine neurons show a phasic response when an unexpected reward is presented. When that reward is reliably predicted by a cue (such as a tone), the dopamine response "shifts" to respond to the cue, and not to the reward. In addition, if now another cue is presented (e.g. a light) that reliably predicts the tone, the animal will learn to respond to the light, and the dopamine response will shift to occur in response to presentation of the light.

These studies suggest that patients with PD should be impaired on tasks which involve this type of learning. This idea is generally consistent with findings of impaired motor sequence learning in PD (e.g. [4,16,21]). However, to date no study has directly examined performance of PD patients on a cognitive task specifically designed to test this idea.

The purpose of the present study was to test this prediction directly, using a 'chaining' task, in which subjects are required to learn a sequence of events leading to reward. The task is constructed such that learning the sequence is accomplished by chaining back associations. For example, if the full sequence to be learned is D → C → B → A → reward, then subjects are first trained to learn A -> reward; then, subjects are trained that B → A which predicts reward, and so forth, until the full sequence leading to reward is learned in this manner.

Based on electrophysiological and computational studies, we predicted that PD patients would show intact learning of a simple stimulus–response association (A → reward). By contrast, PD patients were expected to be impaired when required to learn longer chains.

In addition, we sought to examine the effect of dopaminergic medication on this type of learning by comparing patients tested 'on' or 'off' dopaminergic medication. Patients with PD are most commonly treated with L-dopa, a dopamine precursor which compensates for the loss of striatal dopamine that occurs in the disease [1] and alleviates many of the motor symptoms. Prior studies examining the effect of medication

on cognitive function have led to inconsistent results, with L-dopa sometimes helping, sometimes having no effect, and sometimes worsening cognitive function [14,47,8]. Following prior studies, we explored the effect of medication using a between subject design, comparing patients tested 'on' or 'off' dopaminergic medication. Such an approach is particularly critical in learning and memory studies, where there are significant test-retest effects when comparisons are made within-subjects.

The precise mechanism by which L-dopa elevates dopamine levels is not known. One possibility is that L-dopa leads to global increases in dopamine by inducing dopamine release from non-dopaminergic neurons [26,48,55]. If so, one might predict that L-dopa will not alleviate learning impairments on a "chaining" learning paradigm, since the impairments are presumed to be due to loss of temporally specific dopamine release.

Alternatively, other studies have suggested that L-dopa may enhance dopamine release from remaining neurons in SNc, for example by increasing spontaneous firing [15], or increasing quantal release of dopamine from these neurons [36]. If so, one might expect that L-dopa would remediate patients' performance on a cognitive sequence learning task.

2. Methods

2.1. Participants

Participants included 23 individuals with a diagnosis of idiopathic PD randomly assigned to the 'on' ($n = 12$) versus 'off' ($n = 11$) medication conditions, and 12 age-matched healthy controls. Patients were recruited and diagnosed by a neurologist (J.S.) at the motor disorders clinic at Robert Wood Johnson University Hospital. All patients were in the mild to moderate stages of the disease, with scores on the Hoehn–Yahr scale of motor function [18] that ranged from 1 to 3. All PD patients were non-demented, as indicated by scores greater than 24 on the Mini-Mental State Exam [12]. PD patients were also screened for clinical depression, as indicated by scores below 15 on the Beck Depression Inventory [3]. PD patients were also administered a short battery of neuropsychological tests. The North American Adult Reading Test (NAART; [5]) was used to index cognition; this test involves pronouncing a list of 61 orthographically-irregular words, and the results provide a reliable estimate of verbal IQ [5]. The controlled oral word association test (COWAT) was administered to index executive functioning. In this test, participants are given 1 min to generate as many words as possible beginning with a particular letter; scores are summed across trials with three letters (F, A, S). COWAT performance has been shown to correlate with frontal function (e.g. [22]). The digit span subtest of the Wechsler Memory Scale-Revised (WMS-R; [51]) was administered to index attention and working memory. In this test, participants are required to repeat out loud a list of digits of increasing length,

both forward and backward. There were no significant differences between the 'on' and 'off' groups on any of these measures (*t*-tests, all $P > 0.05$).

All patients included in the study were treated with L-dopa, were stable on their medication doses for at least 3 months, and were responding well to the medication. Patients tested on medication were tested within 3 h since their last dose of medication. Patients tested off medication had refrained from taking medication for a minimum of 16 h. PD patient information is presented in Table 1.

The control group averaged 66.3 years of age (S.D. = 5.3), and 17.1 years of education (S.D. = 2.0). These did not differ significantly from the PD 'on' or PD 'off' groups [ANOVA age × group, $P > 0.1$; education × group $P > 0.1$]. Controls were screened for the presence of any neurological disorder or history of psychiatric illness including depression. All participants were screened for color blindness.

All participants signed statements of informed consent before participating in behavioral testing. All studies conformed to research guidelines established by Rutgers University, Robert Wood Johnson University Hospital, and the Federal Government.

2.2. Behavioral task

In this task, participants were required to learn the correct sequence of colored doors that lead through rooms, with a treasure box hidden behind the last door. Table 2 describes the structure of the task. Example stimuli are shown in Fig. 1.

For each trial, the participant had to choose the correct door from among three colored doors. Initially, participants were required to learn the correct colored door that leads directly to the treasure box (room A). Once that was learned, the participant was taken into room B and required to learn which door leads to room A. Once inside room A, the participant was prompted to choose the correct door that leads to reward. The task thus chains backward learning from rooms A to D, requiring the participant to learn an additional step in the sequence for each phase. Reward was always presented only after the last door (room A) was chosen correctly. When a mistake was made, the participant was shown a brick wall, and then shown the same three doors and prompted to choose the correct door. Each door was uniquely colored, so that there was no overlap in colors between the stimuli in the different rooms (i.e. the same color never appeared in two rooms during training).

Following acquisition of the sequence a probe phase was presented. In the probe phase, the colors of the distracter doors were switched such that for each room, in addition to the correct door for that room, there also appeared a door which was the correct door elsewhere in the sequence, and a door that had never been correct. The purpose of this probe phase was to verify that subjects had learned the series of

Table 1
Clinical characteristics and demographic information for the Parkinson's patients

	Age	Ed.	MMSE	NAART-VIQ	Digit span	COWAT	Hoehn–Yahr (on)	Hoehn–Yahr (at test)	UPDRS (on)	UPDRS (at test)	PD duration
PD 'on'	65.5 (5.3)	17.1 (2.0)	29.1 (0.7)	115.2 (4.7)	12.2 (2.6)	39.3 (11.4)	2.2 (0.54)	2.2 (0.54)	26.4 (4.9)	26.4 (4.9)	6.5 (3.8)
PD 'off'	61.8 (8.8)	17 (3.4)	29.4 (2.1)	117.8 (2.4)	12.3 (1.2)	44.1 (11.0)	2.1 (0.6)	2.59 (0.4)	27.6 (6.0)	40.6 (4.2)	8.45 (4.1)

MMSE: Mini Mental State Exam; NAART: North American Adult Reading Test; COWAT: Controlled Oral Word Association Test; UPDRS: Unified Parinson's Disease Rating Scale; disease duration, age and education (Ed.) in years. S.D. in parentheses.

Table 2
A schematic description of all training phases

Phase	Description	Doors shown	Correct response
Practice	Cue-association	$P_1P_2P_3$	$E_1 \rightarrow \$\$\$$
Chaining	Chain step A	$A_1A_2A_3$	$A_1 \rightarrow \$\$\$$
	Chain step B	$B_1B_2B_3$	$B_1 \rightarrow A_1 \rightarrow \$\$\$$
	Chain step C	$C_1C_2C_3$	$C_1 \rightarrow B_1 \rightarrow A_1 \rightarrow \$\$\$$
	Chain step D	$D_1D_2D_3$	$D_1 \rightarrow C_1 \rightarrow B_1 \rightarrow A_1 \rightarrow \$\$\$$
Probe	Example probe trial	$D_1B_1X_1$	$D_1 \rightarrow C_1 \rightarrow B_1 \rightarrow A_1 \rightarrow \$\$\$$
Retest	Cue-association	$Y_1Y_2Y_3$	$Y_1 \rightarrow \$\$\$$

The phases were trained successively. For each phase, subjects reached criterion performance before moving to the next phase. During the chaining phase, reward was always presented only after subjects completed the entire sequence successfully.

correct stimuli in a sequential manner (i.e. learned the correct door in its correct place in the sequence), rather than having learned the correct stimuli in a non-sequential manner (i.e. learned the correct stimuli but had no knowledge of the chaining relationship between the stimuli). Learning the task in a sequential manner would be expected to result in few to no errors on the probe, since the sequence of correct stimuli had not changed. By contrast, if subjects had learned the correct stimuli, but in a non-sequential manner, they would be expected to make many errors, since in the probe phase a subject had to choose between two stimuli that were both correct at some point in the course of training.

The probe phase was followed by a retraining phase, where subjects were required to learn a new stimulus-reward ($Y \rightarrow$ reward) association with no sequence. The purpose of this phase was to determine whether learning deficits during the sequence phase may be due to fatigue effects on learning single associations.

2.3. Apparatus

Behavioral experiments were automated on a Macintosh iBook computer programmed in the SuperCard language (Al-legiant Technologies, San Diego, CA). Testing took place in a quiet room, with the participant seated in front of the computer at a comfortable viewing distance. The mouse was used throughout the entire experiment.

2.4. Procedure

At the start of the experiment, subjects were told that they would see rooms full of doors, that some of the doors would lead to treasure, and that in each room they should click on the door that they thought would lead to treasure.

On each trial, three different colored doors were presented. For each step in the sequence, the same colored door was always rewarded. Spatial location of the doors was arbitrary and changed randomly between trials. Subjects chose the correct door by clicking on it with the mouse, causing the door to open.

For each of the training phases, subjects were required to make five consecutive correct responses before the next phase began. There was no limit on response time. If a subject went through more than 20 trials without learning the correct response, training of the sequence was terminated, and the subject was taken directly to the last 'retraining' phase of the task.
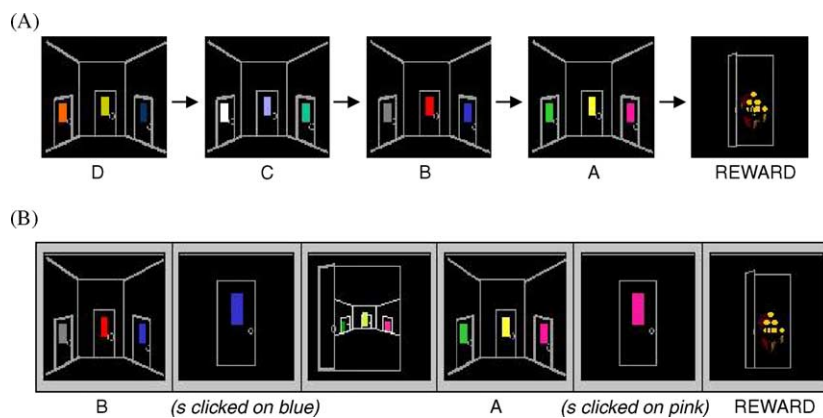

Fig. 1. (A) A schematic presentation of the sequence of doors (phases A–D) leading to the treasure (reward, room A). (B) Sample screen events from two successful trials (Greyscale in figure approximates actual color stimuli in the experiment).

2.5. Practice phase

Subjects were first taken through a practice phase, to familiarize them with the task demands and the mouse. After reaching criterion of five consecutive correct responses, subjects were told that they had successfully finished practice, and that they would now see new doors and should click on the door they thought would lead to treasure.

2.6. Chaining

Phase A: Subjects were shown three doors and required to click on the door they thought led to treasure. If the correct door was selected, the door opened to reveal the treasure.

Phase B–D: After reaching criterion for phase A, subjects were shown a new room, B, with three new colored doors. When the subject clicked on the correct door, the door opened and the subject was taken into the previous room (room A) and prompted to select the correct door to find the treasure. This procedure was replicated in each of the chaining phases, through phase D, with the correct response in each room leading to the next room, until room A, where the correct door led to the treasure.

2.7. Probe

After completing acquisition of the sequence, subjects began the probe phase without prior warning. The procedure for the probe phase was identical to that described for the chaining phase. The only difference was that in the probe phase the colors of the distracter doors for each step in the sequence changed (see Table 2): one distracter door was the same color as the correct door in a different phase of the sequence, and the other door was a novel color which had not previously been shown. A total of six probe trials were presented.

2.8. Retraining

Prior to the retraining phase, subjects were told that they would see a new room with new doors and they should try to find the treasure. This phase was procedurally identical to chaining phase A.

The entire procedure (including practice, training phases A–D, probes, and retraining), took approximately 15–20 min to complete.

2.9. Data collection

On each trial, the computer recorded the selection of colored doors, their spatial ordering, the desired response, and the participant's response. An error was defined as any instance when the subject selected the incorrect door. Since subjects were prompted to reselect the correct door after an error, this meant that a subject could make multiple errors per trial.

3. Results

3.1. Phase A: single stimulus–response associations

All subjects in all groups reached criterion performance on this phase of the task. Controls averaged 0.93 errors (S.E. = 0.23), PD 'on' patients averaged 1.53 errors (S.E. = 0.63), and PD 'off' patients averaged 1.54 errors (S.E. = 0.54). These did not differ significantly [T-test on number of errors, PD 'off' versus controls $t(21) = 1.23$, $P = 0.23$); PD 'on' versus controls, $t(22) = 1.14$, $P = 0.26$].

3.2. Phase B–D: chaining

All control subjects and almost all PD patients in the 'on' medication group were able to learn the full sequence of stimuli. By contrast, PD patients 'off' medication were impaired at learning the full sequence. Percent subjects who reached criterion for each group, for each phase of the sequence, are presented in Fig. 2. Analysis of number of subjects who learned the full sequence for each group revealed that there was a significantly higher failure rate among the PD 'off' group compared to the controls and to the PD 'on' group [Chi-square with Yates correction for small cells $\chi^2(2) = 7.2$, $P < 0.05$]. Specific post hoc pairwise comparisons with alpha adjusted to 0.025 to protect significance levels indicated that while the PD 'off' were significantly impaired compared to controls, [$\chi^2(1) = 5.28$, $P < 0.025$], the PD 'on' were not [$\chi^2(1) = 1.1$, $P = 0.5$].

Analyses comparing those PD 'off' patients who failed at least one phase ('non-learners') versus those that solved all phases ('learners') indicated that these subgroups did not differ significantly in terms of age [learners 59.5 (S.D. = 6.1), non-learners 67.0 (S.D. = 11.5)], education [learners 17.0 (S.D. = 2.2), non-learners 16.1 (S.D. = 2.9)], digit span scores [learners 11.0 (S.D. = 1.4), non-learners 11.6 (S.D. = 0.6)], NAART scores [learners 14.0 (S.D. = 1.4, non-learners 11.0 (S.D. = 5.8)], COWAT scores [learners 48.6 (S.D. = 4.1), non-learners 40.6 (S.D. = 15.0)], MMSE scores [learners 29.4
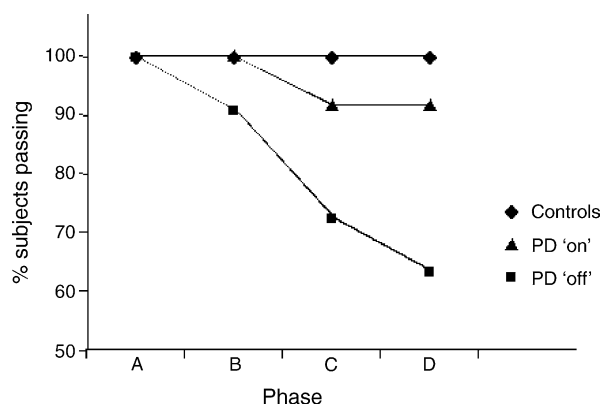

Fig. 2. Percent subjects in each group who successfully reached criterion for each training phase (A–D).

(S.D. = 0.9), non-learners 29.3 (S.D. = 0.8)], or Hoehn and Yahr stage [learners 2.0 (S.D. = 0.5), non-learners 2.3 (S.D. = 0.4)] [independent-samples *t*-tests, all $P > 0.10$]. The difference between the two groups in terms of disease duration was not significant, but was near significance [$t(9) = 2.0$, $P = 0.07$], with non-learners having had PD for more years [11.2 (S.D. = 3.8)] than learners [6.8 (S.D. = 3.6)].

It is interesting to note that among the 'non-learners', failure appeared to be due to difficulty with learning the new stimulus added to that phase (83% of errors), while very few errors were made on stimuli learned in previous phases.

Considering those subjects who successfully completed the sequence (control, $n = 12$; PD 'on', $n = 11$; PD 'off', $n = 7$), a repeated-measure ANOVA on number of errors by group and phase indicated that there were no significant differences between the groups [$F(2, 27) = 1.36$, $P = 0.274$], no significant change in number of errors by phase $F(2, 54) = 1.083$, $P = 0.346$], and no interaction between phase and error [$F(4, 54) = 0.93$, $P = 0.45$].

Classifying errors by 'old' (previously learned stimuli) versus 'new' (stimuli presented in the current phase) confirmed that for all three groups, the large majority of errors were related to learning the new stimuli (PD off, 75% 'new'; PD on, 89% 'new'; controls, 94% 'new'). An ANOVA on proportion of 'new' errors by group indicated that there was no difference between the groups on this measure [$F(2, 32) = 0.182$, $P = 0.4$].

3.3. Probe

Successful probe performance was taken as evidence that subjects had indeed learned the chain of stimuli and displayed sequential knowledge. By contrast, a large number of errors on the probe phase indicated that subjects tended to respond to the correct stimulus, but in its incorrect place in the sequence, suggesting that they may have learned the series of stimuli in a non-sequential manner.

Defining successful probe performance as 1 error or less in the probe phase, 83.3% of control subjects showed successful probe performance. Among the subjects in the PD 'off' group that were able to learn the full sequence, 86% of subjects completed the probe phase successfully. Similarly, among the PD 'on' group, 90% of subjects successfully completed the probe phase. Number of errors on the probe phase did not differ significantly between the groups [ANOVA, $F(2, 32) = 0.182$, $P = 0.8$]. Number of errors for the probe phase are shown in Fig. 3.

3.4. Retraining

All subjects in all groups reached criterion performance on this phase. Fig. 4 shows number of retraining errors for all groups. These did not differ significantly [ANOVA group × errors $F(2, 32) = 0.183$, $P = 0.83$].
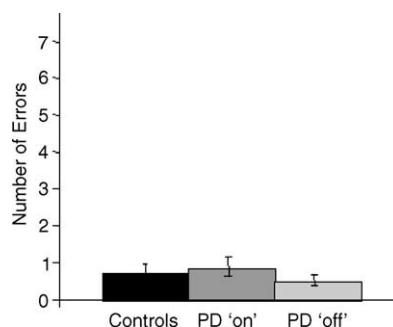

Fig. 3. Mean number of errors for subjects in each group for the probe phase of the task.
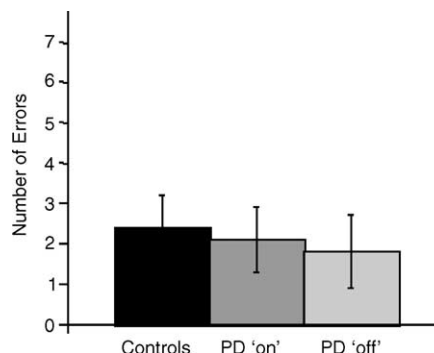

Fig. 4. Mean number of errors for subjects in each group on the last 'retraining' phase of the task.

4. Discussion

The purpose of the present study was to examine performance of individuals with PD on a 'chaining' task, in which a sequence of stimuli leading to a reward is trained backwards, with a new stimulus added in each phase. This learning paradigm is analogous to the kinds of paradigms that involve dopamine signaling in the midbrain [42,46].

As expected, we found that patients with PD tested 'off' L-dopa were impaired at learning the full sequence of stimuli. In particular, a large proportion of PD patients failed to learn sequences longer than 2–3 links. This deficit appeared to be selective to the 'chaining' aspect of the task, since the same patients had no difficulty learning a simple stimulus–response association, either as the first link in the chain, or later in training after having failed to learn the sequence. Further, this deficit was found only in the group of PD patients tested off medication, while among those tested on dopaminergic medication there was no evidence for such a deficit. Interestingly, those PD patients (either 'on' or 'off' L-dopa) that were able to learn the full sequence did so with few errors, and in fact with no more errors than control subjects. Taken together, these findings suggest that PD leads to impairments in learning a 'chaining' task, that this impairment is not found in patients tested on L-dopa, and that overall, this impairment is bi-modal, with subjects either entirely failing to learn the

full length of the sequence, or learning it as well as control subjects.

One difference between learners and non-learners in the present data may be the extent of dopamine cell loss. In support of this idea, the non-learners in our study showed a trend towards having had PD for more years than the learners. In addition, there is individual variability in the extent and topography of cell loss in PD, even when motor scores are similar [11]. In general, early in PD dopamine loss is most prominent in the SNc neurons projecting to the dorsal striatum. However, as the disease progresses, dopamine loss extends more ventrally in the striatum, as well as to the mesolimbocortical dopamine system [23,1]. It is interesting to note that dopamine cells in all of these areas — in the SNc, as well as in the ventral tegmental area (VTA) — display similar reward-related responses during learning [42]. Therefore, it seems plausible that early in PD the mesocorticolimbic dopamine system is able to maintain learning despite severe cell loss in SNc, but that with progression of the disease and extended VTA dopamine cell loss, that ability is further compromised, resulting in failure to learn the sequence. This possibility is particularly compelling given that the ventral striatum is implicated more directly in cognitive function [2], and therefore may play a more critical role in learning to predict cognitive rewards. Given that we have no direct measure of the extent of cell loss in individual subjects, this possibility remains speculative. Future studies directly examining the effect of disease progression on learning, as well as animal models which can directly manipulate the extent and topography of cell loss, would be useful in testing this idea further.

An alternative view of the bi-modal findings may be related to individual differences in learning strategies. Tasks like the one presented here can most likely be learned by multiple learning strategies (e.g. [30]), some of which may be more or less sensitive to basal ganglia disruption. For example, instead of learning to chain the stimuli (i.e. learning associations between the stimuli themselves), subjects could learn the task by associating each stimulus with reward, separately (i.e. learn the correct stimuli, regardless of their place in the sequence). In the probe phase of the task, we sought to distinguish between these possibilities by challenging subjects with trials in which several of the correct stimuli were presented in the wrong place in the sequence, arguing that a subject who had learned the task in a non-sequential manner would make many errors, while a subject who had learned the sequence by 'chaining' between the stimuli would show near perfect performance. We found that 1–2 subjects in each group did in fact appear to learn the task in a non-sequential manner, but this did not differ between the groups. Therefore, it does not appear to be the case that those PD subjects that were able to learn the sequence did so in a non-sequential manner.

This study aimed to test PD performance on a task which relies on chaining back sequences of events leading to reward, in an associative manner. However, an alternative interpretation of the present task may be that subjects did not learn the sequence in an associative manner by chaining between the stimuli one by one, but instead that subjects learned the task by maintaining the correct sequence for each phase in working memory. If so, PD subjects may have failed to learn the full length of the task because the memory load increased as the length of the sequence grew and because working memory abilities are compromised in PD (e.g. [49]).

However, the current data are generally not consistent with a working memory impairment, for several reasons. First, if subjects were indeed learning this task by memorizing or keeping in mind increasingly long sequences, one might predict that the number of trials to criterion would increase for each additional phase of the sequence. However, if subjects learn this task by forming incremental stimulus–response associations in each phase, one might expect that each phase should be learned in approximately the same number of trials; this was is in fact what we found with control subjects in the present study (see Fig. 3). Thus, the fact that control subjects did not show any effect of length of sequence argues against this interpretation. Moreover, working memory deficits in PD are generally found in more progressed patients, and then primarily in spatial working memory, rather than visual working memory which would be necessary for this task [31,32]. In addition, we did not find any evidence of a relationship between measures of frontal function (such as scores on the COWAT, or digit span) and performance on this task.

The finding that PD patients are impaired at learning sequences of stimuli is consistent with a large literature of PD deficits on motor sequence learning tasks (e.g. [21,28]) and motor serial reaction time tasks (e.g. [45,17,10]). Other studies indicate that PD patients may also be impaired on sequence learning tasks that do not rely heavily on a motor response. For example, PD patients were impaired on a verbal version of the serial reaction time test [52]. However, the PD-related impairment on non-motor sequence learning tasks appears to depend on the particular task demands, since other studies have found that PD patients show intact performance on a number of sequence learning tasks [7,17,53]. As with the present study, this ambiguity may be related to the wealth of strategies with which human subjects can approach a learning task. Here, we attempted to gauge the strategies subjects used with probe trials that were administered post-learning and that were designed to gain insight into how subjects had learned the task. An entirely different approach may be to design tasks that constrain as much as possible the strategies with which subjects can learn. Either way, it seems important to take into consideration the flexibility of learning strategies with cognitive learning tasks.

Previous studies of the effect of dopaminergic medication on learning in PD have been few and have led to relatively inconsistent results, with medication sometimes helping, sometimes having no effect, and sometimes impairing learning–depending on the particular task demands and the stage of PD [31,47,8]. Here, we found that L-dopa medication was associated with

substantially better performance on a cognitive sequence learning task.

The precise mechanisms of L-dopa action are not fully understood. Evidence from several studies suggests that L-dopa enhances dopamine levels in the striatum by stimulating dopamine release from non-dopaminergic neurons, most likely via serotonergic-dependent mechanisms [26,48,55]. This possibility seems logical, particularly given the severe loss of SNc dopamine cells in late stages of the disease. However, other studies have indicated that L-dopa may also modulate dopamine release from remaining dopamine neurons. For example, L-dopa enhances spontaneous spike firing in remaining dopamine neurons in a rat model of PD [15]. L-dopa also leads to increased quantal size of dopamine release from midbrain dopamine neurons [36]. These studies suggest a putative mechanism by which L-dopa may contribute to enhanced stimulus-specific signaling, at least in early stage PD. Of particular importance given the present results, these findings suggest that the effect of L-dopa may interact critically with disease progression.

L-dopa has previously been shown to facilitate performance on a variety of tasks which involve attentional shifts, including task switching and alternating fluency [8,14]. These cognitive processes are generally associated with frontal function, and can be viewed as modulatory processes, rather than stimulus-specific reward-based learning. One speculation, therefore, may be that L-dopa leads to enhanced performance on the present task by facilitating alternate, more 'frontal' strategies during learning. In other words, if we assume that the loss of dopamine in PD does in fact lead to difficulty with 'chaining', then perhaps patients tested off L-dopa were more compromised in their ability to turn to other cognitive resources and learning strategies.

Finally, an important issue is the extent to which a cognitive reinforcer can be expected to drive reward-related systems in the human brain. Clearly, one could argue that finding a treasure in a computer game is not equivalent to a food-deprived animal receiving juice. However, there is increasing evidence from functional imaging studies in humans demonstrating that such cognitive rewards do in fact drive reward-related responses in humans. This has been shown with monetary and food rewards, as well as with more abstract positive feedback [9,29,34]. In addition, several researchers have argued that the role of SNc dopamine is not selective to reward-related learning [38]; rather, midbrain dopamine may play an important role in learning by responding to novel behaviorally significant stimuli [20]. If so, the rewarding properties of cognitive stimuli may be of less importance than the novelty and behavioral relevance of the stimuli.

5. Conclusion

In conclusion, mild to moderate stage PD patients show impairments in learning a chain of associations leading to a reward. This impairment is not found in PD patients who are tested 'on' L-dopa. There are individuals with PD who are able to successfully learn a chain of associations leading to reward (either 'on' or 'off' L-dopa) as well as controls, suggesting individual variability in learning strategies and/or the extent and topography of dopaminergic cell loss. PD patients that failed to learn the sequence had a tendency towards longer disease duration, suggesting that extensive dopamine loss may contribute to this deficit, while the overall better performance of PD patients tested on L-dopa suggests the replenishment of dopamine with medication alleviates it.

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