

# Cognitive sequence learning in Parkinson's disease and amnesic mild cognitive impairment: Dissociation between sequential and non-sequential learning of associations

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## Abstract

Evidence suggests that dopaminergic mechanisms in the basal ganglia (BG) are important in the learning of sequential associations. To test the specificity of this hypothesis, we assessed never-medicated patients with Parkinson's disease (PD) and amnesic mild cognitive impairment (aMCI) using a chaining task. In the training phase of the chaining task, each link in a sequence of stimuli leading to reward is trained step-by-step using feedback after each decision, until the complete sequence is learned. In the probe phase of the chaining task, the context of stimulus-response associations must be used (the position of the associations in the sequence). Results revealed that patients with PD showed impaired learning during the training phase of the chaining task, but their performance was spared in the probe phase. In contrast, patients with aMCI with prominent medial temporal lobe (MTL) dysfunctions showed intact learning during the training phase of the chaining task, but their performance was impaired in the probe phase of the chaining task. These results indicate that when dopaminergic mechanisms in the BG are dysfunctional, series of stimulus-response associations are less efficiently acquired, but their sequential manner is maintained. In contrast, MTL dysfunctions may result in a non-sequential learning of associations, which may indicate a loss of contextual information.

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## 1. Introduction

Ample evidence suggests that the medial temporal lobe (MTL) and the basal ganglia (BG) play a distinct role in learning and memory. The MTL, including the hippocampus, is important in declarative memory functions, whereas the BG is essential for learning habits and skills, such as simple associations between stimuli and responses (Squire, Stark, & Clark, 2004; Yin & Knowlton, 2006). Although the MTL may not be critical in

simple stimulus-response learning, it is important in more complex situations when stimuli are presented in a novel context (Eichenbaum, Mathews, & Cohen, 1989; Knowlton, Mangels, & Squire, 1996; Myers et al., 2002, 2003). For example, one can easily learn that pressing a blue switch leads to the turning on of the air conditioner in the bedroom (trial-by-error stimulus-response learning based on feedback). However, it is possible that, in the kitchen (novel context), pressing a blue switch has a different outcome. In this case, the stimulus-response habit may lead to erroneous consequences.

In patients with Parkinson's disease (PD), Shohamy, Myers, Grossman, Sage, and Gluck (2005) demonstrated that dopaminergic mechanisms in the BG are involved in the learning of

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sequential (“chaining”) associations, in which each link in a sequence of stimuli leading to reward is trained step-by-step using feedback after each decision, until the complete sequence is learned. In PD, cellular death in the substantia nigra pars compacta (SNc) leads to the depletion of dopamine in the BG (Hornykiewicz & Kish, 1987). In addition to the motor symptoms, this results in a variety of cognitive dysfunctions, with a special reference to habit learning which is based on trial-by-error choices, feedback, and reward. Frank, Seeberger, and O’Reilly (2004) and Frank (2005) proposed that in unmedicated PD patients the low level of dopamine in the BG is not sufficient for reward during positive feedback, whereas in PD patients receiving L-dopa substitution, dopamine “overshoots” disrupt learning about the absence of reward during negative feedback (see also Shohamy, Myers, Geghman, Sage, & Gluck, 2006). In this respect, the chaining task is informative because patients with PD, tested off their normal dopaminergic medication perform more poorly on this task than patients with PD who receive L-dopa substitution (Shohamy et al., 2005), which suggests that L-dopa ameliorates sequential association learning deficits.

During the chaining task, participants were required to learn a sequence of events leading to reward (Shohamy et al., 2005). In the first phase of this task, the screen showed a room (Room 1) with three doors (A, X, Y), each bearing a colored card; the participant was required to choose one of these doors. A correct response (door A) led to a treasure chest (reward), while an incorrect response (X or Y) led to a brick wall, and subjects had to try again. Once this A → reward association was learned, participants were presented with another room (Room 2) with three new colored doors (B, W, Z). An incorrect response (W or Z) led to a brick wall, while a correct response (door B) led to Room 1, where subjects would again choose the correct door (A) to reach the reward. Once this new association (B → A → reward) was learned, a new room was added to the sequence, until eventually the participant learned a full sequence: D → C → B → A → reward. Shohamy et al. (2005) found that PD patients, tested off their normal dopaminergic medication, were normal at learning simple, one-step associations (e.g., A → reward), but increasingly impaired at further learning as the length of the chain increased.

The chaining task also contained a probe phase, which was designed to test stimulus-response habits in novel contexts. After the learning of the chain of associations, the colors of the incorrect doors were switched such that in each room, in addition to the correct door of that room, there also appeared a door which was the correct door elsewhere in the sequence. Thus, for example, in Room 2, the subject might be presented with a choice between door B (correct), A (incorrect at this point in the sequence), and X (never correct). The probe phase was designed to verify that participants learned the correct door in its correct place in the sequence (learning in a sequential manner). A participant who had learned the sequence should always make the correct response (choose door B in Room 2), regardless of what other doors are present. But if the participant learned the correct door but had no knowledge of its place in the sequence (an absence of contextual knowledge), then in Room 2, subjects might mistakenly choose door A, which had also been associ-

ated with reward. Such learning would be equivalent to simple stimulus-response learning: that is, choose door A wherever it appeared, choose door B wherever it appeared, etc. Using such a strategy, patients could master the learning phase—since during the learning phase doors A and B only ever appeared at the correct step in the sequence. However, such a strategy would not lead to good performance in the probe phase, where both the previously rewarded doors A and B might appear in the same room, and additional information about the context (position in the sequence) would be required to disambiguate the correct response.

Among those unmedicated PD patients who were able to learn the full, four-step chain, Shohamy et al. (2005) found probe performance averaged less than one error per 24 responses, an error rate that was not significantly different from controls.

In the present study we had two aims. First, we used an updated version of the Shohamy et al. (2005) chaining task to investigate whether never-medicated PD patients would show a similar learning impairment to that shown in Shohamy et al. (2005) for PD patients withdrawn from their normal dopaminergic medication. We predicted that, like Shohamy et al.’s (2005) unmedicated patients, our never-medicated PD patients would show impaired performance on learning of chained associations due to low levels of dopamine in the BG.

Second, to investigate the role of the MTL on this task, we also considered a group of patients with amnesic mild cognitive impairment (aMCI), which is considered a transitional state between normal aging and Alzheimer’s disease. Patients with aMCI show relatively spared general cognitive abilities and daily functioning, but their declarative memory functions are impaired as compared with age-matched controls, presumably due to impaired MTL function (Collie & Maruff, 2000; Gauthier et al., 2006; Petersen et al., 1999). We predicted that our aMCI patients would learn the chaining task successfully, but due to their putative MTL dysfunction, we expected that they might be impaired at the probe phase of the task, which tests whether subjects have learned the correct responses in the right context, making each response at the correct point in the series.

## 2. Methods

### 2.1. Participants

Twenty healthy controls, fourteen patients with aMCI, and sixteen never-medicated patients with PD (Hoehn-Yahr stages: I–IV, median: 2.8) participated in the study. The diagnosis of aMCI was established according to the Mayo Clinic Alzheimer’ Disease Research Center criteria (Petersen et al., 1999). Exclusion criteria were other neurological or psychiatric disorders, substance misuse disorders, head trauma, vascular lesions on routine head MRI scans, and medications affecting central nervous system functions. All subjects received background neuropsychological testing including verbal IQ (Wechsler, 1981), Mini-Mental State Examination (MMSE), Rey Auditory Verbal Learning Test (RAVLT), Boston Naming Test (BNT), and semantic fluency (SF) test (Lezak, 1995). These tests are especially sensitive for aMCI, and deficits on these tests correlate with the subtle pathology of the MTL, parietal lobe, and frontal lobe (Rose et al., 2006). After a complete description of the study, a written informed consent was obtained from each participant, and the study was done in accordance with the Declaration of Helsinki.

## 2.2. The “Kilroy” chaining task

### 2.2.1. Stimuli and screen events

The “Kilroy” chaining task was an updated version of the one presented in Shohamy et al. (2005). The original version of the task was programmed from a “first-person” or “player-oriented” point of view, so that the screen approximated a camera moving through the rooms with, for example, doors getting bigger as the viewpoint approached them. Some older patients had trouble understanding this viewpoint. In the current (“Kilroy”) version of the task, there is now an animated character that moves through the rooms and opens doors. The subject’s task is to guide this character through the rooms to a goal point, the outside world. Otherwise, the task is the same as presented in Shohamy et al. (2005).

The task was run on a Macintosh computer, and programmed in the SuperCard language. On each trial of the experiment, the animated character (nicknamed “Kilroy”) appears in a room with three doors; each door has a colored card (see Fig. 1A). The rooms have a uniform white background, and are drawn using perspective lines, with three black doors appearing on the far wall. The doors appear about 2” high, and the colored cards are each 1” high by 0.5” wide, and outlined in white for visual clarity. The animated figure (Kilroy) appears about 2” tall.

For each subject, the colored cards marking the doors in each of six rooms are selected from a set of eighteen unique colors, so that the same three colors appear each time Kilroy enters a particular room, but no color appears in more than one room during training. Thus, for example, room A might have red, green, and purple doors; room B might have yellow, blue, and brown doors; and so on. Spatial layout of these three colors on the doors (left, center, right) is randomized on each trial, so that the correct answer (left, center, right) varied

across trials in a room; only the location of the color card indicated which was the correct response. Colors were highly discriminable and assignment of colors was randomized across subjects.

In each room, the subject uses the computer mouse to move the cursor to click on one of the doors. When the subject selects a door, a few additional drawings of Kilroy appear to approximate a rough animation showing Kilroy turning, walking to the door, and trying to open it. If the subject’s choice is incorrect, the door is “locked” and Kilroy cannot open it; he puts his hands on his hips and makes a disappointed face, and the word “Locked!” appears on the bottom of the screen (Fig. 1B). Kilroy then moves back to the center of the room, and awaits the subject’s next choice. If the subject’s choice is correct, Kilroy opens the door and steps through. If this room was at the end of the chain, Kilroy reaches the outside, where he turns and gives a thumbs-up sign (Fig. 1C); if the room was at an earlier stage of the chain, Kilroy steps through into the next room (Fig. 1D) and, once there, waits for further instructions (as in Fig. 1A). In either case (correct or incorrect response), the outcome appears on the screen for 1 s; there is then a 0.33 s interval before Kilroy appears at the bottom of the screen again, ready for new instructions. There is no limit on response times.

One trial consists of Kilroy traversing a full sequence of rooms until (eventually) reaching the outside. The length of this sequence increases from one to four rooms over the course of training. A trial is scored as correct if the subject chooses the correct door on the first opportunity for every room in the chain; however, a subject may make one or more errors on a trial by choosing an incorrect door one or more times before choosing the correct door, in each of one or more rooms in the chain. This means that a subject could make more than one error per trial. Each learning phase continues until the subject completes four consecutive correct trials or to a maximum of fifteen trials. If a subject fails to

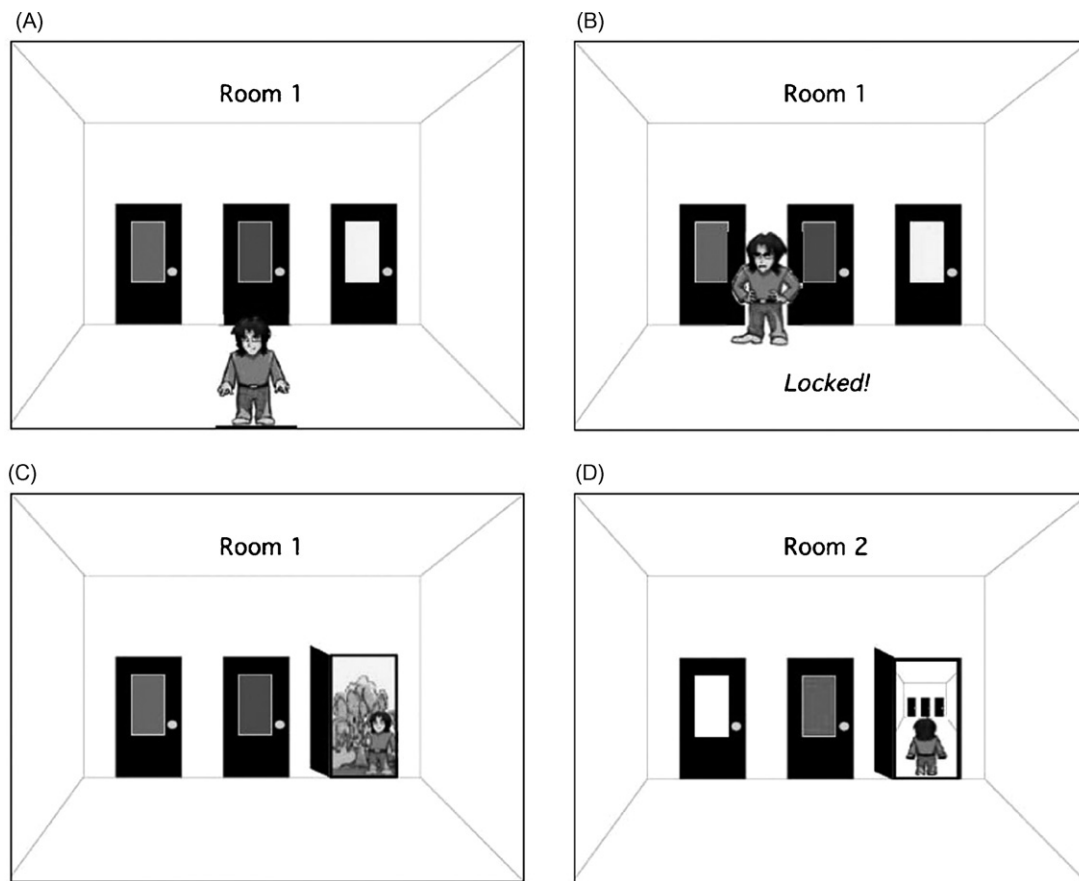


Fig. 1. Sample screen events during the “Kilroy” chaining task. On each trial, the subject’s task is to navigate an animated figure (nicknamed “Kilroy”) through one or more rooms to reach the outside world. In each room, exactly one door is unlocked; on any trial, the colored cards hanging on each door signal which door is currently unlocked. (A) At the start of a trial, Kilroy appears in a room with three doors, each bearing a colored card. The subject clicks on one of the doors, and Kilroy moves to try to open that door. (B) If the subject’s choice was incorrect, the door is locked. (C) If the subject’s choice was correct, and the room was at the end of the chain, Kilroy opens the door and steps through to the outside. (D) If the subject’s choice was correct, but the room is not at the end of the chain, Kilroy opens the door and steps through into another room containing three different doors, where he awaits further instructions (as in (A)).

reach criterion within the maximum number of trials for any phase, that phase is terminated, further training and probe phases are skipped, and the subject proceeds directly to the last (retraining) phase of the task.

### 2.3. Procedure

The subject is seated in a quiet testing room at a comfortable viewing distance from the screen. Before the test, the subject is informed that the aim of the game is to help a cartoon figure get out of the house as many times as possible. The following instructions appear: “Welcome to the experiment. In this experiment, you will see a character named Kilroy who is trying to get out of the house. Each room in the house has three doors, and each door has a colored card on it. On each trial, two of the doors are locked, and one door is unlocked. In each room, click on the color card of the door that you think is unlocked. If you are correct, Kilroy will get outside. Good luck!” The test then consisted of the following parts:

1. *Practice.* The Practice Room appears, with three colored doors, and Kilroy in his “waiting-for-instructions” position at the front bottom of the screen. If the subject chooses the correct door, Kilroy makes it outside and the trial is concluded. Every trial terminates with Kilroy (eventually) reaching the outside. The practice phase continues until the subject makes four consecutive correct trials (i.e. chooses the correct door on the first response in each of four trials).

2. *Sequence training.* At this point, new instructions appear: “You’ve successfully finished practice! Now Kilroy will be put in some new rooms. Again, in each room, two doors are locked and one door is unlocked. Each time, click on the door that you think is unlocked. Sometimes, Kilroy will have to go through more than one room to reach the outside. Good luck!”

Kilroy now appears in his “waiting-for-instructions” position in Room 1. This phase is identical to the Practice phase, except that three new colored cards are used. Here, subjects have to learn to open the correct door (A). Once this is learned, phase 2 begins, in which Kilroy appears in Room 2, which contains three new colored cards; here, choice of the correct door (B) leads Kilroy to Room 1, where a correct answer leads him outside. Once this is learned, subjects work through phase 3 (door C in Room 3 leads to Room 2 and so on) and phase 4 (door D in Room 4 leads to Room 3 and so on) until, by the end of phase 4, subjects should be choosing the correct door in each room:  $D \rightarrow C \rightarrow B \rightarrow A \rightarrow$  reward.

3. *Probe phase.* Next comes a probe phase, un signaled to the subject. At the start of a trial, Kilroy appears in Room 4. Correct responses will, as usual, allow him to progress through the sequence of rooms and reach the outside. Now, however, the colored cards are switched. In each room, one of the three cards is always the correct answer in that room, at that point in the sequence; one of the cards is always a choice that was correct in a different room; the third card (distracter) is a choice that was never correct in any room. Thus, in Room 2, Kilroy might be presented with a choice between card B, card A, and card X. Card B is the correct choice, and should be chosen by a subject who had learned the chain: that is, what choice to make at each step in the sequence. But a subject who had merely learned non-sequential stimulus-response associations might choose A, since that is a stimulus that had been directly associated with reward in the past. The probe phase contained six trials, each trial consisting of a trip through the usual four rooms.

In the probe phase, the participant may commit three types of errors. “Reward error” is when the participant chooses the door at the end of the chain which had previously been directly associated with reward, but chooses it at the wrong point in the sequence (i.e., choosing door A in any room other than Room 1). “Chaining error” is when the participant chooses any other previously correct door (B, C, or D) but chooses it at the wrong point in the chain (e.g., choosing door C instead of door B in Room 2). “Distracter error” is when the participant chooses a door (e.g., X or Y) that has never been right at any point in the sequence.

4. *Retraining phase.* Finally came a retraining phase, in which subjects are required to learn a new room with three new colored cards, one of which leads directly to the outside. The purpose of this phase was to determine whether any learning deficits observed on the sequence learning or probe phase were due to fatigue effects or other non-associative factors. At the end of the test, the subject sees a screen reporting the total number of trials on

which Kilroy got out, which is equal to the total number of trials (regardless of intervening errors).

### 2.4. Data analysis

The STATISTICA 6.0 package was used for data analysis (StatSoft, Inc., Tulsa). First, data were entered into Kolmogorov–Smirnov tests and Levene’s tests in order to check the normality of distribution and homogeneity of variance, respectively. In the case of normal distributions and homogeneous variances, parametric tests were used, whereas if data deviated from normal distribution or variance was not homogeneous, non-parametric tests were included (Kruskal–Wallis analysis of variance (ANOVA) and Mann–Whitney *U*-tests). ANOVAs were followed by *F*-tests for planned comparisons and Tukey’s HSD tests for post-hoc comparisons. The level of significance was set at  $\alpha < 0.05$ .

## 3. Results

### 3.1. Demographic parameters and background neuropsychology

The three experimental groups did not differ in age, years of education, or verbal IQ ( $p > .1$ ) (Table 1). The Kruskal–Wallis ANOVA conducted on the MMSE scores revealed a significant main effect of group ( $H(2) = 10.62, p = .005$ ). As compared with controls and patients with PD, patients with aMCI showed significantly lower MMSE scores (Mann–Whitney *U*-tests,  $Z = 2.82, p = .005$  and  $Z = 2.73, p = .006$ , respectively). There was no significant difference between controls and patients with PD ( $p > .5$ ) (Table 1).

The ANOVA conducted on the RAVLT scores revealed a significant main effect of group ( $F(1, 47) = 25.38, p < .0001$ ). Tukey’s HSD tests indicated that patients with aMCI displayed lower RAVLT scores as compared with controls ( $p < .001$ ) and with patients with PD ( $p < .001$ ). There was no significant difference between controls and patients with PD ( $p > .4$ ) (Table 1).

The ANOVA conducted on the BNT scores revealed a significant main effect of group ( $F(1, 47) = 5.22, p < .05$ ). Tukey’s HSD tests indicated that patients with aMCI were impaired as compared with controls ( $p < .05$ ), but not as compared with patients with PD ( $p > .1$ ). Controls subjects and patients with PD did not differ ( $p > .5$ ) (Table 1).

The ANOVA conducted on the SF scores revealed a significant main effect of group ( $F(1, 47) = 5.57, p < .05$ ). Tukey’s HSD tests indicated that patients with aMCI were impaired

Table 1  
Demographical parameters and background neuropsychology

	Controls ( $n = 20$ )	PD ( $n = 16$ )	aMCI ( $n = 14$ )
Age (years)	69.3 (9.5)	68.4 (8.7)	71.0 (10.3)
Male/female	14/6	11/5	8/6
Years of education	12.5 (2.3)	13.0 (5.1)	12.9 (4.6)
Verbal IQ	107.2 (10.4)	109.9 (11.6)	108.0 (12.9)
MMSE	28.7 (1.2)	28.8 (1.5)	27.2 (1.4)
RAVLT	50.5 (3.2)	48.8 (4.4)	40.1 (5.5)
BNT	53.3 (3.9)	51.7(3.0)	48.9(5.0)
SF	17.6 (3.8)	16.3 (3.4)	13.4 (3.8)

PD, Parkinson’s disease; aMCI, amnesic mild cognitive impairment; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; BNT, Boston Naming Test; SF, semantic fluency.



as compared with controls ( $p < .05$ ), but not as compared with patients with PD ( $p > .08$ ). Controls subjects and patients with PD did not differ ( $p > .5$ ) (Table 1).

In summary, aMCI patients were impaired relative to controls on several measures of memory and cognition, consistent with their diagnosis; PD patients showed no cognitive or memory impairments on these tests.

### 3.2. “Kilroy” chaining task

The ANOVA conducted on the number of errors in the four training phases revealed a significant main effect of group ( $F(1, 42) = 8.87, p < .001$ ) and training phases ( $F(3, 126) = 11.30, p < .0001$ ). The interaction between group and training phases was significant ( $F(6, 126) = 3.75, p < .01$ ). However, this interaction was not significant when controls were compared with patients with aMCI using an  $F$ -test for linear trend ( $p = .4$ ). In contrast, the group by training block interaction was significant when controls were compared with patients with PD ( $F(1, 42) = 13.04, p < .001$ ) and when patients with aMCI were compared with patients with PD ( $F(1, 42) = 14.63, p < .001$ ). Tukey’s HSD tests confirmed that patients with PD were impaired in this phase of the chaining task as compared with controls ( $p < .01$ ) and with patients with aMCI ( $p < .005$ ). According to the Tukey’s HSD tests conducted on the group by training phase interaction, this difference was significant only in the fourth training phase ( $p < .005$ ). Control subjects and patients with aMCI did not differ ( $p > .4$ ) (Fig. 2). For all groups, in all training phases, such mistakes as did occur tended to occur on the first room in a trial—in other words, on the newest, least-practiced door; later in the trial, confronted with well-practiced rooms and doors, subjects tended to make very few errors.

The ANOVA conducted on the number of errors in the probe phase revealed a significant main effect of group ( $F(1, 42) = 6.75, p < .01$ ). Tukey’s HSD tests revealed that patients with aMCI committed more errors than controls ( $p < .05$ ) and

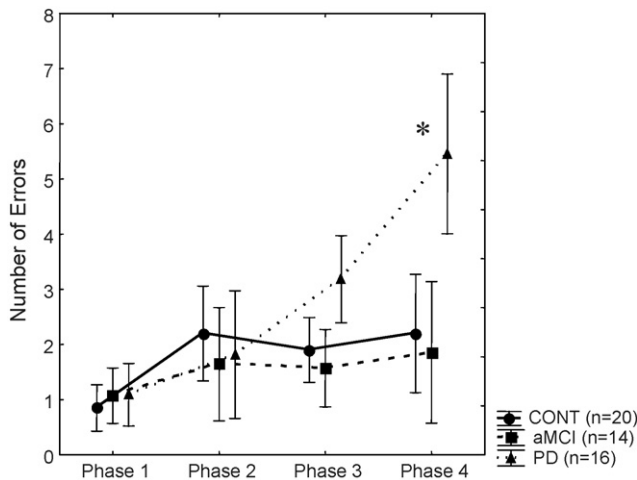


Fig. 2. Mean number of errors in the four phases of the training phase of the “Kilroy” chaining task. Error bars indicate 95% confidence intervals. CONT, controls; aMCI, amnesic mild cognitive impairments; PD, Parkinson’s disease. \* $p < .005$  (CONT vs. PD and aMCI vs. PD), Tukey’s HSD tests.

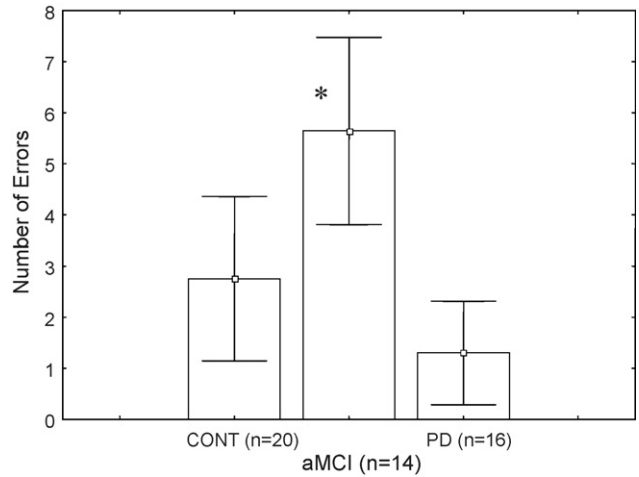


Fig. 3. Mean number of errors in the probe phase of the “Kilroy” chaining task. Error bars indicate 95% confidence intervals. CONT, controls; aMCI, amnesic mild cognitive impairments; PD, Parkinson’s disease. \* $p < .05$  (CONT vs. aMCI) and  $p < .005$  (aMCI vs. PD), Tukey’s HSD tests.

than patients with PD ( $p < .005$ ). Control subjects and patients with PD did not differ ( $p > .4$ ) (Fig. 3). However, the absence of a group difference in total number of errors on the probe phase might conceivably mask a difference in the types of errors made by each group on the probe phase. To examine this, we analyzed the different types of errors in the probe phase (“reward”, “chaining”, and “distracter” errors). The ANOVA revealed no significant main effect of group ( $p = .6$ ), indicating that the distribution of different types of errors were similar across groups (Fig. 4). Finally, on the retraining phase, the control group averaged 1.1 errors ( $SD 1.7$ ), the PD group averaged 1.2 errors ( $SD 1.0$ ), and the aMCI group averaged 1.1 errors ( $SD 0.9$ ); these group differences fell short of statistical significance (ANOVA,  $p > .5$ ).

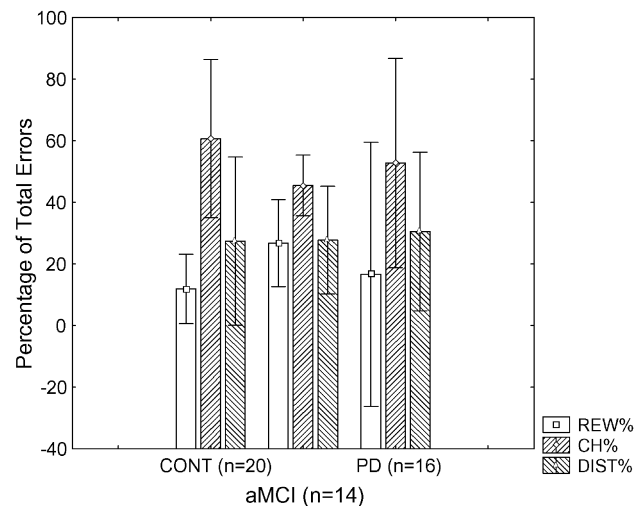


Fig. 4. Mean percentage of different types of errors in the probe phase of the “Kilroy” chaining task. Error bars indicate 95% confidence intervals. REW, reward; CH, chaining; DIST, distracter; CONT, controls; aMCI, amnesic mild cognitive impairments; PD, Parkinson’s disease.

#### 4. Discussion

To summarize the results, on the chaining task, PD patients were not impaired at learning a simple response, as evidenced by their good performance both in phase 1 of training and on the retraining phase, but showed impairment at learning the full sequence, evident in their poor performance on phase 4 of training. This could not be attributed to simple fatigue, as they showed good performance on a later retraining phase. Patients with aMCI, in contrast, learned as well as controls.

Our results are consistent with the view that patients with PD show substantial learning deficits on tasks requiring trial-by-error, feedback-based stimulus-response learning, especially when sequences or chains of associations must be acquired (Shohamy et al., 2005). Importantly, as in the prior paper, the PD patients were not impaired at learning or maintaining a single stimulus-response association, as evidenced by their intact performance both on the first room of the chain and in the retraining phase; it was only at longer chain lengths that they evinced impairment. Thus, the PD impairment cannot easily be attributed to either difficulty discovering the correct answer, nor maintaining that response; it may be attributable to executive or working memory functions insofar as longer chain lengths require maintaining increasing numbers of correct responses in memory at once. Our finding is generally consistent with other studies finding normal performance by PD patients on some simple stimulus-response associations. PD patients might show normal performances, but it highly depends on the general and perceptual demands of the task, medication effects, and on the severity of symptoms (Shohamy et al., 2004; Swainson et al., 2006). The prior paper by Shohamy et al. (2004) considered PD patients who had been withdrawn from their normal dopaminergic medication for a period of about 12 h, and were thus in a relatively dopamine-depleted state; however, this prior paper could not rule out long term consequences of dopaminergic medication, such as neuroplastic changes in synapses and receptors in the BG. In addition, although L-dopa does have a half-life consistent with a return of symptoms about 12 h post-administration, 12 h is not necessarily enough to wash all of the drug from the patient's system. Since our patients with PD had never received dopaminergic medications, their learning deficit could not be associated with such potential long-term changes in the BG associated with L-dopa medication, nor with sudden changes in dopaminergic tone. Therefore, our results provide stronger evidence that the deficit both in our never-medicated PD patients and in Shohamy et al.'s dopamine-depleted PD patients is likely to be directly due to decreased dopamine level in the BG.

In contrast to our patients with PD, patients with aMCI exhibited intact learning on the training phase of the "Kilroy" chaining task. The neuropsychological profile of our patients with aMCI was highly similar to other samples reported in the literature (Rose et al., 2006). In general, patients with aMCI exhibit prominent episodic memory impairment as compared with other domains of cognition, and sophisticated neuroimaging methods reveal subtle alterations in the MTL of such patients (Fellgiebel et al., 2006; Muller et al., 2005; Rose et al., 2006; Stoub et al.,

2006), reflecting a high vulnerability for Alzheimer's disease which develops in 12% of these patients per year (Gauthier et al., 2006; Petersen et al., 1999). The preserved learning in our aMCI sample would be consistent with other findings demonstrating that MTL damage generally does not impair the ability to learn simple, non-declarative stimulus-response associations (Knowlton et al., 1996; Myers et al., 2002, 2003; Squire et al., 2004). The fact that aMCI patients showed intact learning during the training phase argues against the possibility that the deficit of PD patients during this phase is fully attributable to generalized cognitive dysfunction, particularly in light of the generally poorer performance by our aMCI than PD patients on the neuropsychological testing.

The most intriguing finding was that, in contrast to patients with PD who exhibited normal performance during the probe phase of the chaining task, patients with aMCI committed significantly more probe errors than controls. This finding seems to be counterintuitive, because one may expect that learning a sequence may not be independent of reproducing a sequence. The probe phase was intended to verify that participants had learned the correct door in its correct place in the sequence, encoding not only the correct door but also its context (the room in which it occurred). It would be possible to learn this task in a non-sequential fashion: that is, by learning to choose door A whenever it appeared, and to choose door B whenever it appeared, and so on—without encoding the context in which these doors occurred. This simple context-free strategy would allow a subject to complete the acquisition phase, but would lead to errors on the probe phase, where both doors A and B could appear together, and contextual information was needed to disambiguate which door was the correct choice.

Consistent with the prior findings of Shohamy et al. (2005), our control and PD patients, after mastering the acquisition phase, made few errors on the probe phase, indicating they had encoded contextual information in their initial learning. PD patients showed more errors than controls during feedback learning, but once they passed the criterion of the acquisition phase, they were able to reproduce the sequence. In contrast, patients with aMCI—who had acquired the task quickly during feedback learning—made many more probe errors. This deficit would be consistent with MTL dysfunction in these patients, since many studies have documented that MTL function is important in the representation of context especially in the case of higher-order associations (e.g., Ergorul & Eichenbaum, 2006). However, it is important to note that, in most aMCI patients, brain abnormalities are not fully circumscribed to the MTL, and other brain structures than the MTL are also affected (Rose et al., 2006). Therefore, our data cannot completely rule out the possibility that context representation problems in the aMCI group are due to the dysfunction of other structures than (or in addition to) the MTL. Future work to investigate chaining and probe performance in patients with bilateral MTL damage would help elucidate the specific role of the MTL in the aMCI patients' impaired contextual performance. In the meantime, these results are consistent with prior findings that non-demented elderly patients with hippocampal atrophy are spared at learning multiple simple stimulus-response associations, but impaired

when familiar information is presented in a new context, involving either new stimulus features or new stimulus combinations (Myers et al., 2002, 2003).

In summary, we found a double dissociation between sequential and non-sequential learning of chaining associations. Patients with PD with BG impairment showed deficient feedback-guided learning of associations (training phases of the “Kilroy” chaining task), but if they once learned these associations, their knowledge extended to the contextual features of stimulus-response associations (probe phase of the “Kilroy” chaining task). In contrast, aMCI patients with prominent MTL pathology efficiently learned stimulus-response associations during feedback-guided training, but their performance was erroneous when probed for contextual information. These data suggest that BG plays an important role in trial-by-error, feedback-guided learning of stimulus-response associations, whereas the MTL is necessary for the representation of the sequences of associations, particularly the context in which particular responses will be reinforced.

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