Distinct Hippocampal and Basal Ganglia Contributions to Probabilistic Learning and Reversal

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Abstract

■ The hippocampus and the basal ganglia are thought to play fundamental and distinct roles in learning and memory, supporting two dissociable memory systems. Interestingly, however, the hippocampus and the basal ganglia have each, separately, been implicated as necessary for reversal learning—the ability to adaptively change a response when previously learned stimulus–outcome contingencies are reversed. Here, we compared the contribution of the hippocampus and the basal ganglia to distinct aspects of learning and reversal. Amnesic subjects with selective hippocampal damage, Parkinson subjects with disrupted basal ganglia function, and healthy controls were tested on a novel probabilistic learning and reversal paradigm. In this task, reversal can be achieved in two ways: Subjects can reverse a previously learned response, or they can select a new cue during the reversal phase, effectively ''opting out'' of the reversal. We found that both patient groups were intact at initial learning, but differed in their ability to reverse. Amnesic subjects failed to reverse, and continued to use the same cue and response learned before the reversal. Parkinson subjects, by contrast, opted out of the reversal by learning a new cue–outcome association. These results suggest that both the hippocampus and the basal ganglia support reversal learning, but in different ways. The basal ganglia are necessary for learning a new response when a previously learned response is no longer rewarding. The failure of the amnesic subjects to reverse their response or to learn a new cue is consistent with a more general role for the hippocampus in configural learning, and suggests it may also support the ability to respond to changes in cue–outcome contingencies. ■

INTRODUCTION

Studies of the neural bases of learning and memory suggest that the medial-temporal lobe (MTL) and the basal ganglia each play fundamental and distinct roles in learning and memory, supporting two dissociable ''memory systems'' (Gabrieli, 1998; Robbins, 1996; Squire, 1987). Extensive evidence suggests that the MTL (including the hippocampus and surrounding cortices) supports rapid learning of relations between stimuli, often referred to as episodic or declarative memory (Eichenbaum & Cohen, 2001; Eichenbaum, 2000; Schacter & Wagner, 1999; Myers & Gluck, 1994; Cohen & Eichenbaum, 1993; Squire, 1987). Evidence, to date, suggests that the basal ganglia play a distinct and complementary role supporting implicit, incremental, feedback-based learning of stimulus–response associations, often referred to as procedural or habit learning (Gabrieli, 1998; Knowlton, Mangels, & Squire, 1996; Robbins, 1996).

In humans, one paradigm that has been used to assess the distinct roles of the basal ganglia and the MTL in learning is probabilistic category learning. In a commonly used version of this task, subjects learn to predict a category outcome (e.g., ''sun'' or ''rain'') based on four visual cues (e.g., cards with geometric shapes). The relationship between the cues and outcomes is probabilistic so that each individual cue is only partially predictive of the outcome. Because of this probabilistic nature, performance is optimally achieved by incremental learning of cue–outcome associations over many trials (Shohamy, Myers, Grossman, Sage, Gluck, & Poldrack, 2004; Gluck, Shohamy, & Myers, 2002; Knowlton et al., 1996).

Initial neuropsychological studies demonstrated that patients with basal ganglia disruption (due to Parkinson disease) are impaired at probabilistic learning, whereas amnesic subjects (with MTL or diencephalic damage) were intact early in learning, but impaired later (Knowlton et al., 1996). Amnesic subjects with selective hippocampal damage due to hypoxia are impaired at probabilistic learning both early and late (Hopkins, Myers, Shohamy, Grossman, & Gluck, 2004).

These patterns of spared versus impaired learning may be related to distinct roles for the MTL and the basal ganglia in qualitatively different learning strategies

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(Shohamy, Myers, Onlaor, & Gluck, 2004; Gluck et al., 2002). Use of mathematical models to obtain detailed analyses of response profiles revealed that patients with Parkinson disease tend to rely on nonoptimal, single-cue strategies throughout learning (Shohamy, Myers, Onlaor, et al., 2004). Amnesic subjects with hippocampal damage failed to consistently apply any strategy during learning, as opposed to both healthy controls and Parkinson patients (Hopkins et al., 2004).

Neuroimaging (fMRI) data also show MTL/basal ganglia dissociations in healthy controls during probabilistic learning. These studies indicate that the MTL and the basal ganglia may competitively interact during probabilistic learning (Poldrack et al., 2001; Poldrack, Prabhakaran, Seger, & Gabrieli, 1999). Furthermore, both imaging and patient work indicate that whether learning is guided by MTL or basal ganglia activity has important consequences for the ability to flexibly use learned associations in a new context (Foerde, Knowlton, & Poldrack, 2006; Shohamy, Myers, Geghman, Sage, & Gluck, 2006; Myers et al., 2003). Specifically, MTL-based learning affords subsequent flexible use of what was learned, whereas basal ganglia-based learning does not. These findings are consistent with a growing body of data from animals and humans indicating a critical role for the hippocampus in building flexible mnemonic representations that support the ability to generalize learned associations to novel contexts and stimuli (Heckers, Zalesak, Weiss, Ditman, & Titone, 2004; Preston, Shrager, Dudukovic, & Gabrieli, 2004; Eichenbaum & Cohen, 2001; Dusek & Eichenbaum, 1997; Cohen & Eichenbaum, 1993).

Despite evidence dissociating MTL and basal ganglia contributions to learning (Shohamy & Wagner, in press), cumulative evidence implicates both systems in the cognitive processes associated with reversal. Reversal involves the ability to adapt one's response to a stimulus when the stimulus-response contingency becomes inverted. For example, in probabilistic learning, a cue that was initially associated with one outcome 80% of the time will now be associated with the other outcome 80% of the time. Thus, reversal learning relies on the ability to flexibly change a previously established stimulus–response association when a prior response is no longer rewarding.

Extensive evidence suggests that the basal ganglia and the frontal cortex contribute to reversal learning (Frank & Claus, 2006). For example, neurons in the ventral striatum reverse their reward-related responses in reversal learning paradigms (Setlow, Schoenbaum, & Gallagher, 2003). fMRI studies in humans also reveal ventral striatal activity during reversal in a probabilistic reversal task (Cools, Clark, Owen, & Robbins, 2002). Furthermore, damage to the striatum leads to impairments on reversal learning, in animals (Schoenbaum & Setlow, 2003; Annett, McGregor, & Robbins, 1989) and in patients with Parkinson disease (Cools, Altamirano, & D'Esposito, 2006; Cools, Barker, Sahakian, & Robbins, 2001; Swainson et al., 2000). In Parkinson disease, the reversal learning deficit is exacerbated by dopaminergic medication (Cools et al., 2001, 2006; Swainson et al., 2000), as are other forms of feedback-based incremental learning (Shohamy et al., 2006; Frank, Seeberger, & O'Reilly, 2004). These data are consistent with a more general role for the basal ganglia and midbrain dopamine system in supporting incremental, feedback-based learning of stimulus–response associations (Shohamy et al., 2006; Delgado, Miller, Inati, & Phelps, 2005; Seger & Cincotta, 2005; Frank et al., 2004; Shohamy, Myers, Grossman, et al., 2004; Shin & Ivry, 2003).

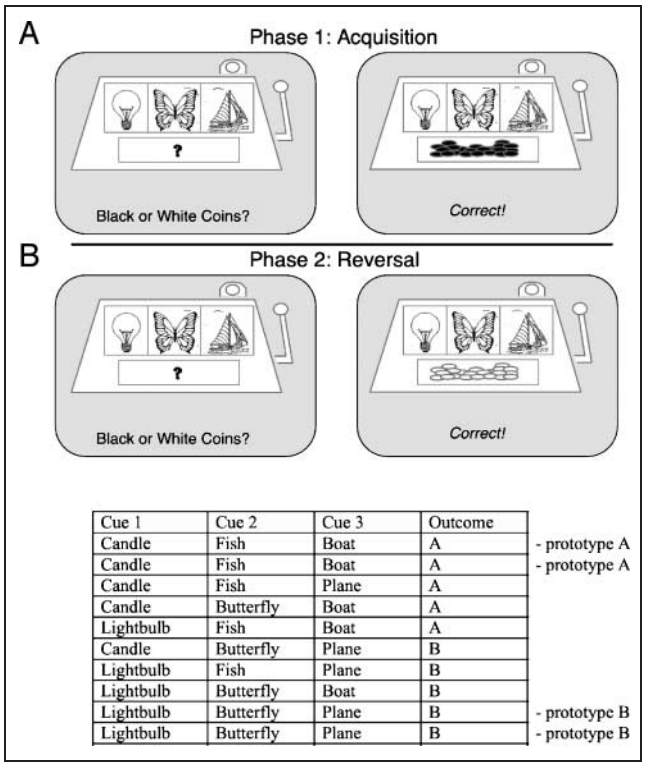
Converging evidence also implicates the MTL, and specifically the hippocampus, in reversal learning. In animals, hippocampal lesions impair reversal learning (Marston, Everitt, & Robbins, 1993; Fagan & Olton, 1986; Berger & Orr, 1983; Zola & Mahut, 1973). Similarly, amnesic patients with bilateral hippocampal damage have intact performance on initial discrimination learning but are subsequently impaired on reversing the learned stimulus–outcome mappings (Myers, Deluca, Hopkins, & Gluck, 2006; Carrillo et al., 2001; Myers, Hopkins, Kesner, Monti, & Gluck, 2000). Amnesic patients have been found to make more perseverative errors compared to controls and continue to apply a previous response rule even after the reversal (Myers et al., 2006).

Why precisely the hippocampus is necessary for reversal remains an open question. However, one possibility is that reversal learning may involve the kind of flexibility thought to be a hallmark of hippocampal memory representations (Foerde et al., 2006; Eichenbaum & Cohen, 2001; Cohen & Eichenbaum, 1993). By this view, reversal learning is essentially a form of transfer or generalization, which involves the ability to flexibly retrieve and use a previously learned association once the contingencies have changed. If so, damage to the hippocampus might impair reversal, just as it otherwise impairs the ability to flexibly use learned associations under novel circumstances.

Taken together, these data suggest that both the basal ganglia and the MTL are necessary for reversal learning, although each system may contribute to distinct aspects of reversal learning. However, as MTL and basal ganglia contributions to reversal have previously been assessed independently, and with different paradigms, many questions remain regarding the specific contribution of each brain region. Furthermore, it is unknown how reversal learning relates to other characteristics of the MTL versus the basal ganglia in learning, such as how performance on reversal relates to learning strategies and to the flexible use of the learned associations once cue–outcome contingencies change. Understanding the dissociated contributions of the MTL versus the basal ganglia to reversal learning is fundamental to our understanding of the cognitive role of these two memory systems in learning.

The purpose of the present study was to examine hippocampal versus basal ganglia contributions to learning

and reversal using a novel paradigm that allows a direct assessment of learning strategies and flexibility. Subjects with basal ganglia disruption due to Parkinson disease, and subjects with hippocampal damage due to hypoxic brain injury were tested on a probabilistic classification task. Sample task events and cue–outcome probabilities are shown in Figure 1. This task is broadly similar to previous category learning tasks sensitive to basal ganglia and hippocampal contributions (Shohamy, Myers, Grossman, et al., 2004; Shohamy, Myers, Onlaor, et al., 2004; Poldrack et al., 2001; Knowlton et al., 1996), with several key modifications, as follows. First, the present task was designed to be easier, in order to ensure learning prior to reversal: Three cues were always presented on each trial (rather than a varying number of cues on each trial, as in previous designs), each cue could take on one of two values, and each independently predicted the correct outcome on 80% of trials (rather than a range of differing probabilities between .2 and .8, as in previous designs). Thus, simply by attending to any one cue (a ''single-cue'' strategy), a subject could learn to correctly predict the outcome on 80% of trials. Second, based on prior findings of basal ganglia contributions to multicue patterns versus single cues (Shohamy, Myers, Onlaor, et al., 2004), we further designed the task such that the *pattern* or configuration of the three cues on any trial was a perfect predictor of the outcome. Thus, by attending to the configuration of cues (a ''pattern'' strategy), a subject could correctly predict the outcome on every trial. Finally, acquisition was followed by an unsignaled reversal phase, during which the previous cue–outcome associations were reversed, with each cue now predicting the opposite outcome on 80% of trials, and each pattern now predicting the opposite outcome on 100% of trials. Thus, although this novel task shares with previous studies the need to learn probabilistic cue–outcome relations, the specific design is, in fact, quite different, suggesting it may involve differential cognitive and neural processes. Indeed, converging data suggest that the specific nature of the probabilistic relations, as well as the specific task demands, can dramatically impact the cognitive and neural processes supporting probabilistic learning (Shohamy, Myers, Kalanithi, & Gluck, 2008; Foerde et al., 2006; Shohamy, Myers, Grossman, et al., 2004; Poldrack et al., 2001; Fagan & Olton, 1986).



Cue 1	Cue 2	Cue 3	Outcome	
Candle	Fish	Boat	A	- prototype A
Candle	Fish	Boat	A	- prototype A
Candle	Fish	Plane	A	
Candle	Butterfly	Boat	A	
Lightbulb	Fish	Boat	A	
Candle	Butterfly	Plane	B	
Lightbulb	Fish	Plane	B	
Lightbulb	Butterfly	Boat	B	
Lightbulb	Butterfly	Plane	B	- prototype B
Lightbulb	Butterfly	Plane	B	- prototype B

Figure 1. Subjects were told they were playing a slot machine, where their job was to predict whether the outcome would be black or white coins. (A) On each trial, subjects were presented with three visual cues, made a response, and received response-contingent feedback. Acquisition was followed by a surprise reversal, where stimulus–response contingencies were reversed. (B) Cue–outcome structure for the acquisition phase; the reversal phase was identical but with outcomes reversed. Each of the three cues was 80% predictive of each outcome, and the three-cue pattern was 100% predictive of the outcome. Each block of 100 trials included 10 each of the trial types except for the two prototype patterns (candle–fish–boat and lightbulb–butterfly–plane), which appeared 20 times per block.

The present design allowed the reversal to be performed in two different ways: (a) having encountered unexpected negative reinforcement, subjects could learn to reverse their prior response while maintaining the same response rules used during acquisition (analogous to a standard reversal paradigm). Following the sample trials in Figure 1, a subject who had learned that the presence of the butterfly cue predicts black coins, would now reverse that response and learn that the butterfly predicts white coins. Alternatively, (b) in the present design reversal could be supported by flexibly selecting a new cue that is different from that used during learning. For example, when the butterfly cue is no longer predictive of black coins, rather than reversing that association, a subject could now learn a new cue–outcome association (e.g., that the sailboat cue predicts white coins). In this way, subjects could ''opt out'' of the reversal and simply learn a novel association.

We administered this task to a group of amnesic patients with bilateral hippocampal damage, a group of Parkinson patients with basal ganglia dysfunction, and matched controls. To quantitatively assess how damage to the hippocampus and basal ganglia affects learning and reversal under these circumstances, we used mathematical models to determine which learning strategies subjects engaged in during acquisition and reversal, and whether these strategies differed in controls and in the patient groups. We predicted that both Parkinson and amnesic subjects would be impaired at reversal learning. Prior studies led us to predict that amnesic subjects would perseverate following the reversal. In contrast, Parkinson patients were expected to have difficulty

reversing; however, given an intact MTL system, we hypothesized that they may be able to flexibly use what they had learned to master the task by ''opting out'' of the reversal and learning a new stimulus–outcome association.

METHODS

Subjects

Parkinson Patients and Controls

Thirteen individuals with a diagnosis of idiopathic Parkinson disease were recruited, including 10 men and 3 women, with a mean age of 62.4 years (*SD* = 3.9) with a mean education level of 16.8 years (*SD* = 2.8). Degree of Parkinsonism ranged from Hoehn & Yahr (H–Y) Stages 1–3, with a time since onset ranging from 2.5 to 19 years (mean = 9.0 years).

All Parkinson patients were screened for the absence of dementia and depression by the referring neurologist. Additionally, patients were required to score greater than 26 on the Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975), an estimate of intact cognitive function and absence of dementia; the group mean was 29.6 (*SD* = 0.5). Depression screening included the Beck Depression Inventory II (Beck, 1987), cutoff = 12 and/or the Centers for Epidemiologic Studies Depression Scale (Radloff, 1977), cutoff = 16.

All Parkinson patients were on dopaminergic medication at time of testing. Eight were treated with L-dopa alone, two with dopamine agonists alone (pramipexole), and three were treated with a combination of both. None were on anticholinergic medication or on antidepression medication.

Fifteen healthy controls were recruited to match the Parkinson patients, including six men and nine women, with a mean age of 63.1 years (range = 57–68, *SD* = 3.3), and a mean education of 16.2 years (range = 12–22, *SD* = 3.3). Neither age nor education differed significantly from the Parkinson group (independent-samples *t* tests, all $p > .100$). Control subjects were screened for the absence of any neurological or psychiatric disorder, including depression (BDI or CES-D), and were free of any medication that could impair cognition. The control group averaged 29.8 on the Mini-Mental State Exam, which did not differ from the Parkinson group (independent-samples *t* test, $p > .500$).

Amnesic Patients and Controls

Nine amnesic patients with bilateral hippocampal damage due to hypoxic brain injury were recruited, including two women and seven men. The patients' mean age was 43.1 years (*SD* = 9.1), with a mean education level of 13.4 years (*SD* = 1.7). All amnesic patients were at least 1-year postinjury at time of test. The amnesic patients were recruited and tested at LDS Hospital, Salt Lake City, Utah ($n = 8$) and University of Medicine and Dentistry of New Jersey/Kessler Center for Rehabilitation, New Jersey ($n = 1$). Extensive neuropsychological evaluation indicated that the amnesic subjects had normal intelligence, but impaired memory on measures of verbal and visual memory, consistent with their classification as amnesics.

Quantitative magnetic resonance (MR) imaging was available in seven of the nine amnesic subjects, confirming (a) bilateral hippocampal damage but (b) no temporal lobe damage. Images from a representative control and three of the amnesic patients are shown in Figure 2. MR images were acquired at 1.5 Tesla with a quadrature head coil using standard clinical protocols. Sagittal T1-weighted (500/11/2; TR/TE/excitations) images were first acquired followed by axial proton density and T2-weighted (3000/31; 90/1) spin-echo images. Slice thickness was 5 mm with a 2-mm interslice space. Images were acquired on a 256 × 192 matrix with a 22-cm field of view for the axial images and a 24-cm field of view for the sagittal images. The coronal images were 3-mm-thick interleaved sections with a field of view of 22 cm on a 512 × 256 matrix. Quantitative MR analyses of the hippocampus and the temporal lobe were performed on all hypoxic patients as per the methods described previously (Bigler et al., 1997). Hippocampal volumes were measured in the coronal slices (Bigler et al., 1997). Intrarater and interrater reliability exceeded .90. The amnesic subjects' hippocampal volumes ranged from 2 to 5 standard deviations below age-matched means. Total

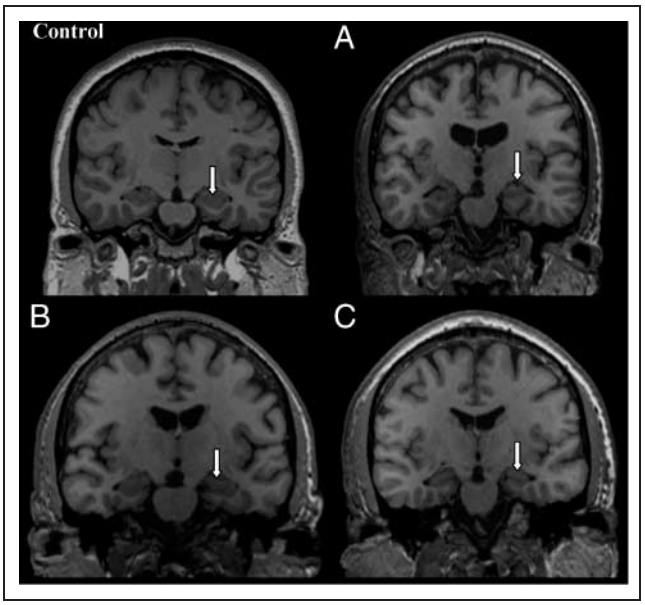


Figure 2. Representative magnetic resonance scans of amnesic and control subjects. T1 coronal view through the body of the hippocampus in a representative control subject, and (A–C) hypoxic subjects with bilateral hippocampal atrophy (arrow points to the hippocampus), and enlargement of the temporal horns of the lateral ventricles. Scans shown in radiological view (left/right reversal).

hippocampal volumes (right and left) were significantly decreased in the amnesic subjects relative to controls ($F = 12.0, p = .005$). There was no difference in temporal lobe volumes for amnesic subjects compared to controls ($p = .159$).

Fifteen healthy controls were recruited to match the amnesic subjects including nine women and six men, with a mean age of 47.4 years ($SD = 8.1$) and a mean education level of 15.4 years ($SD = 3.3$). Control subjects were screened for the absence of any neurological or psychiatric disorder, including depression (BDI or CES-D), and were free of any medication that could impair cognition (e.g., anticholinergics, antidepressants). The control group did not differ significantly from the amnesic group on age, education, nor on an estimate of premorbid IQ (NAART VIQ) (independent-samples t test, all $p > .50$). On verbal memory, the controls did not differ from the amnesics on immediate paragraph recall (Logical Memory I; $p = .47$), but did differ on delayed paragraph recall (Logical Memory II; $p < .01$); on pictorial memory, the groups did not differ on ROCFT copy ($p = .21$), but the controls scored significantly higher than the amnesics on both immediate and delay ROCFT (all $p < .01$). The controls also performed significantly better than the amnesic subjects on measures of frontal and executive function, including the COWA FAS, Trails A and B, and digit span (all $p < .05$). These results confirm dense memory impairments in the amnesic subjects, with some frontal executive impairments.

Stimuli and Category Structure

On each trial, the computer screen showed a slot machine with three windows (Figure 1). Each window could show one of two icons. For example, the left window could show a picture of a candle or a lightbulb, the center window could show a picture of a fish or a butterfly, and the right window could show a picture of a boat or a plane (Figure 1). Thus, there were eight distinct patterns that could appear, as shown in Figure 1. Within each block of 10 trials, each pattern appeared once in random order, with two presentations of the ''prototype'' patterns (candle–fish–boat and lightbulb–butterfly–plane). Each pattern was deterministically associated with an outcome. Thus, for example, the probability of Outcome A given the candle–fish–boat pattern was 1.0, whereas the probability of Outcome B given the lightbulb–butterfly–plane pattern was 1.0.

The pattern structure shown in Figure 1 also shows that each individual cue was associated with one outcome with 80% probability. Thus, for example, the candle occurred with Outcome A on 80% of trials, and with Outcome B on 20% of trials. The candle–fish–boat and lightbulb–butterfly–plane patterns are prototypes because they contain all three cues associated with one of the categories.

Procedure

The experiment was conducted on a Macintosh G3 or iBook computer with color screen, programmed in the SuperCard language (Solutions Etcetera). The keyboard was masked except for two keys, labeled ''black'' and ''white,'' which the subject used to enter responses.

After informed consent was obtained, subjects were seated in a quiet testing room at a comfortable viewing distance from the screen. On each trial, the subject saw the slot machine with one of the three-cue patterns showing and had to guess whether this pattern would return white or black coins (corresponding to Category A or B). The subject inputs a response by pressing one of two keys labeled ''black coins'' and ''white coins.'' The correct answer was then displayed in the form of coins in the tray. If the subject's answer was correct, the score bar incremented, a high tone was played, and a smiley face appeared at the top of the score bar. If the subject's answer was incorrect, the score bar decremented, a low tone was played, and a frowning face appeared at the bottom of the score bar. Example screen events are shown in Figure 1.

The acquisition phase consisted of 100 trials, with trial order randomized. At this point, without warning to the subject, the reversal occurred so that patterns which had previously returned white coins now returned black coins, and vice versa. Reversal continued for 100 trials with the new contingencies.

Data Collection

On each trial, the computer recorded the stimuli, the subject's response, and the actual outcome. The subject's response was defined as correct if it matched the correct outcome for that pattern.

Strategy Analysis

Strategy analysis followed the general procedures described previously for probabilistic category learning (Shohamy, Myers, Onlaor, et al., 2004; Gluck et al., 2002). In brief, we considered two basic classes of strategy that subjects might use during the acquisition phase on this task. In the ''pattern strategy,'' subjects could learn to predict categories based on complete patterns (combinations of three cues), and could achieve 100% correct responding. In the ''one-cue'' strategy, subjects could learn to predict strategies based on whether a single cue was present: for example, ''respond A whenever the candle is present and B otherwise,'' or ''respond B whenever the butterfly is present and A otherwise.'' Because each single cue is 80% predictive of the outcome, a subject could achieve 80% correct performance using a one-cue strategy based on any one of the three cues.

Although it would theoretically be possible for a subject to respond based on a combination of two cues

(e.g., ''respond A whenever candle and fish are present''), this type of strategy could at best produce 70% correct responding. No subject's data were well described by this strategy, and we did not consider this strategy further.

For the pattern strategy, it was possible to compute ideal data consisting of the expected responses on each trial if the subject was following that strategy. For each of the three possible one-cue strategies (based on candle–lightbulb, fish–butterfly, or boat–plane), we similarly computed ideal data consisting of the expected responses if the subject was following that strategy. We then compared each individual subject's actual responses against these ideal data and classed the subject as having followed a pattern strategy or a one-cue strategy, based on which more closely approximated the subject's actual performance. In other words, the model accounting for the greatest percentage of responses for each subject was considered the best fit.

Because it is also possible that no strategy may provide a valid fit to an individual's response pattern, we also considered an ''other'' category of responses, which included response patterns that were consistent with random guessing, or else with the use of some unknown other strategy. A subject's responses were classified as ''other'' in the case where at least 60% of their responses were not accounted for by either the ''one-cue'' or the ''pattern'' strategies. There were no cases in the data for which subjects had perfectly overlapping fits to two different strategies.

For the reversal strategy, we again classed subject strategies as ''pattern,'' ''one-cue,'' or ''other,'' but in addition, we considered a ''perseverative'' strategy, under which a subject would continue to respond using the same strategy and response mappings that had been used during acquisition. This would lead to 0% correct responding for subjects using a pattern strategy or 20% correct responding for subjects using a one-cue strategy. Thus, being fit by a perseverative strategy was orthogonal to being fit by any of the other strategies. Our expectation was that a perseveration strategy might initially describe performance immediately following reversal, but that subjects (particularly healthy controls) would quickly abandon this strategy once it ceased to result in a positive outcome.

Finally, for the reversal strategy, we also considered whether a subject was using the same specific cue during acquisition and reversal, but simply reversed their response, or whether subjects selected a new cue during the reversal, and learned a new stimulus–response association. An example for someone using the same cue would be a subject that had used a one-cue strategy, using the middle cue, during acquisition, and who was also best fit by a one-cue strategy, using the middle cue, during the reversal. Similarly, an individual fit by a pattern strategy during both acquisition and reversal would be classified as using the same strategy in acquisition and reversal. An example for a subject who shifted to a new cue during reversal would be a subject who used a one-cue strategy, using the middle cue, during acquisition, and who was also best fit by a one-cue strategy, but using a different specific cue, during the reversal. Thus, classification of subjects along this dimension (same vs. new cue in reversal) was independent of subjects' classification as using a one-cue or pattern strategy in either of the phases. This approach allowed us to classify subjects as staying with the same cue during acquisition and reversal, or as adopting a new strategy, or new cue, during the reversal relative to acquisition.

RESULTS

Figure 3 shows behavioral performance by each patient group and matched controls over the course of acquisition and reversal. After 100 acquisition trials, performance improved across all groups, and there were no significant differences between patients and controls. Among the Parkinson patients and their controls, a repeated measures ANOVA revealed an effect of Block

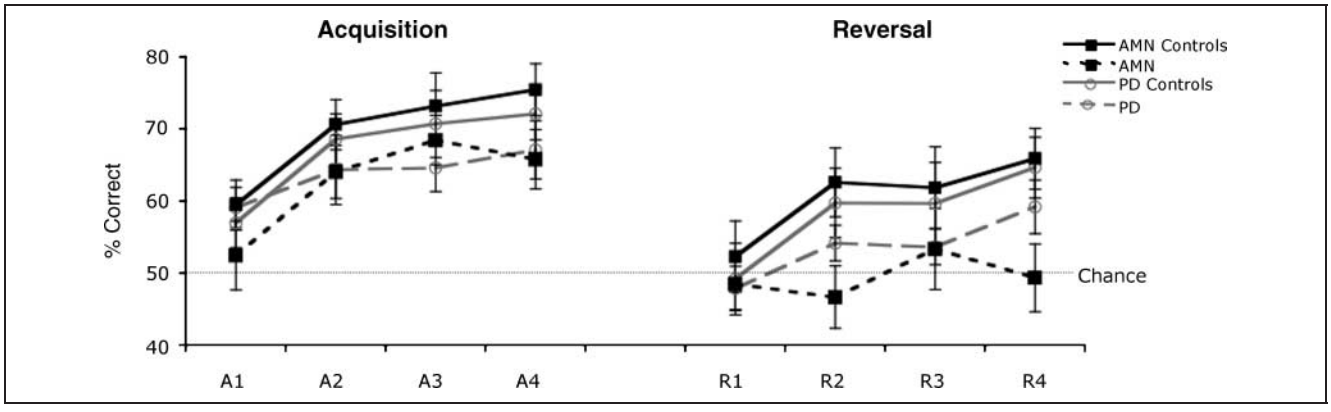


Figure 3. Performance among Parkinson patients (PD), amnesic subjects (AMN), and their matched controls, on probabilistic learning and reversal. All groups acquired the initial associations, but the groups dissociated in their response to the reversal.

[$F(3, 72) = 2.91, p < .05$], with no main effect of Group [$F(1, 24) = 0.64, p = .43$] nor a Group × Block interaction [$F(3, 72) = 0.11, p = .98$]. Similarly, among the amnesics and controls, there was a main effect of Block [$F(3, 48) = 16.16, p < .001$], with no main effect of Group [$F(1, 16) = 2.70, p = .11$] nor a Group × Block interaction [$F(3, 41) = 0.43, p = .73$].

Given prior data showing impaired probabilistic learning in Parkinson disease (Shohamy, Myers, Onlaor, et al., 2004; Knowlton et al., 1996), we conducted separate t tests on only the last block of acquisition to fully explore the possibility of differences in learning. This difference was not significant for either of the patient groups compared with their controls, although there was a trend for such an effect among the amnesics [t test comparing Block 4 performance for the Parkinson patients vs. controls, $t(24) = 0.58, p = .57$; for the amnesics and controls, $t(16) = 1.91, p = .07$]. Given the sample size, we further calculated effect size for the main effect of group for both groups, revealing an effect size of 0.3 for the Parkinson patients versus controls and 0.7 for the amnesics versus controls.

Immediately following reversal, performance in all groups declined, as indicated by worse performance during the first block of reversal compared with the last block of acquisition, with no differences between the patient and control groups in the extent of this decline [repeated measures ANOVA, Parkinson vs. controls, Block: $F(1, 24) = 43.34, p < .001$; no main effect of Group: $F(1, 24) = 0.31, p = .58$; no Group × Block interaction: $F(1, 24) = 1.49, p = .23$; Amnesics vs. controls, Block: $F(1, 16) = 32.85, p < .001$; no main effect of Group: $F(1, 16) = 2.57, p = .13$; no Group × Block interaction: $F(1, 16) = 0.86, p = .37$].

During the reversal phase, Parkinson patients and controls improved their performance, with no difference between them. A repeated measures ANOVA revealed a main effect of Block [$F(3, 72) = 12.88, p < .001$], with no main effect of Group [$F(1, 24) = 2.15, p = .12$] nor a Group × Block interaction [$F(3, 72) = 0.22, p = .64$].

By contrast, the amnesics were significantly impaired at reversal. A repeated measures ANOVA revealed a main effect of Group [$F(1, 16) = 3.286, p < .05$] and a main effect of Block [$F(3, 48) = 1.51, p < .05$], with no Group × Block interaction [$F(3, 48) = 2.076, p = .12$]. Analyses of effect sizes were consistent with these results: The main effect of group for the Parkinson patients versus controls was 0.55, whereas it was 0.8 for the amnesics versus controls.

To further explore learning across the reversal phase, we conducted a regression analysis on performance by block for each of the patient groups. This analysis confirmed that although the Parkinson patients showed significant learning during the reversal phase, the amnesics did not [Parkinson patients, $F(1, 51) = 4.95, p < .05$; amnesics, $F(1, 35) = 0.353, p = .556$].

Finally, we examined whether the performance of the amnesics differed between acquisition and reversal. A repeated measures ANOVA on Phase (acquisition vs. reversal) × Group (amnesics vs. controls) revealed a main effect of Phase [$F(1.22) = 31.23, p < .001$], a main effect of Group [$F(1, 22) = 4.31, p < .05$], and no Phase × Group interaction [$F(1, 22) = 1.22, p = .28$].

Strategy Analysis

Strategy analyses sought to determine whether each subject's choice patterns were driven more by a single-cue, by the three-cue pattern, or by neither, and whether subjects used the same strategy during acquisition and reversal or instead ''opted out'' of the reversal by shifting strategies. Strategy analysis followed the general procedures described previously (Shohamy, Myers, Onlaor, et al., 2004; Gluck et al., 2002), and are detailed in the Methods section. Briefly, strategies were determined by comparing each individual's trial-by-trial responses against the ''ideal'' response expected if a subject were strictly adhering to one of the examined strategies. Subjects for whom one of the considered strategies did not provide a fit of at least 60% of their responses was classified as using an ''other'' strategy, which also included subjects who were just guessing.

Strategy distribution during the acquisition phase is shown in Figure 4. During the 100 trials of acquisition, most subjects were best fit by a one-cue strategy, suggesting they responded based on a single cue; this was the case for Parkinson subjects, amnesic subjects, and both control groups. The difference in distribution between one-cue versus pattern did not differ between any of the groups (chi-square tests, all $p > .1$). Among those best fit by a one-cue strategy, approximately half the subjects were using the cue that appeared in the middle (51.4%), whereas 18.9% used the cue on the left, and

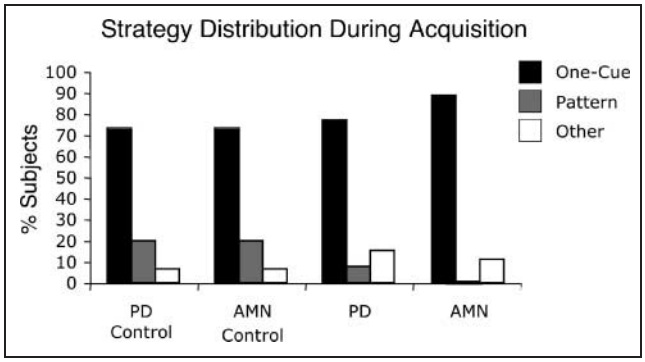


Figure 4. Distribution of individual subjects in each group according to model-based analyses of learning strategies during acquisition. Most subjects in all groups learned based on a single cue (a ''one-cue'' strategy), and only a few subjects responded based on the three-cue pattern (''pattern'' strategy). PD = Parkinson; AMN = amnesics.

29.7% used the cue on the right. This distribution across cues differed significantly ($\chi^2 = 6.054$, $df = 2$, $p < .05$).

To examine the possibility that subjects switched strategies during learning, we also analyzed strategies in the first block versus last block of acquisition. This analysis showed that most subjects used a one-cue strategy during the first and last blocks of acquisition (during the first block of acquisition, 73.3% of Parkinson controls, 73.3% of amnesic controls, 100% of amnesic subjects, and 76.9% of Parkinson subjects were best-fit by a one-cue strategy; during the last block of acquisition, 66.6% of Parkinson controls, 73.3% of amnesic controls, 88.8% of amnesic subjects, and 76.9% of Parkinson subjects were best-fit by a one-cue strategy). Subjects' reliance on single cues is likely due to the fact that (a) each individual cue was highly predictive of the outcome, and (b) paying attention to two cues would lead to worse performance (at best 70%) than a single-cue strategy (80%), possibly preventing subjects from trying to learn the (optimal) full pattern strategy.

In the reversal phase, we examined strategies during the first and last blocks. In addition to the one-cue and pattern strategies, we considered a perseverative strategy, defined as subjects' continued use of the *same cue and same response* as used during the acquisition. During the first block of reversal, perseverative responding accounted for responses of approximately half of the subjects in each group, as shown in Figure 5. A chi-square analysis of strategy (perseverative vs. one-cue or pattern) by group in the first reversal block revealed no significant differences in strategy distribution between each of the patient groups and their respective controls (Parkinson vs. controls, $\chi^2 = 0.03$, $df = 1$, $p > .8$; amnesics vs. controls, $\chi^2 = 1.5$, $df = 1$, $p > .2$). By the last block of reversal, most of the controls and Parkinson subjects were no longer responding perseveratively. By contrast, the majority of amnesic subjects were still perseverating during the last block of reversal. This difference in strategy distribution among the groups in the last block of reversal was significant (perseverative vs. one-cue or pattern strategies, among amnesics vs. controls, $\chi^2 = 5$, $df = 1$, $p < .05$; among amnesics vs. Parkinson, $\chi^2 = 4.5$, $df = 1$, $p < .05$), indicating a significantly greater proportion of perseverative subjects among the amnesic subjects than among their controls or the Parkinson subjects.

Finally, we explored whether subjects continued to use the same cue in reversal, but reversed the response, or whether during the reversal they learned a new cue–outcome association based on a different cue or different strategy. As shown in Figure 6, most of the controls stayed with the same cue in the reversal as they had used during acquisition, merely swapping the valences. Similarly, almost all of the amnesic subjects continued to use the same cue during reversal as during acquisition, consistent also with the findings of increased perseveration in this group. By contrast, most of the Parkinson subjects ''opted out'' of the reversal, shifting to responses that followed a new cue in the reversal phase. Thus, Parkinson subjects tended to shift cues more than controls, whereas amnesic subjects tended to shift cues less than controls. The difference in distribution of subjects using a new cue in reversal versus staying with the same cue in reversal was significant (Parkinson vs. their controls, chi-square test, $\chi^2 = 7.26$, $p < .01$; Parkinson vs. amnesics, $\chi^2 = 3.7$, $p = .05$). Those Parkinson patients that used a new cue during the reversal performed better on the last reversal block than those that did not select a new cue [66.62% correct vs. 47.20% correct, respectively; independent-samples t test, $t(11) = 3.57$, $p < .005$].

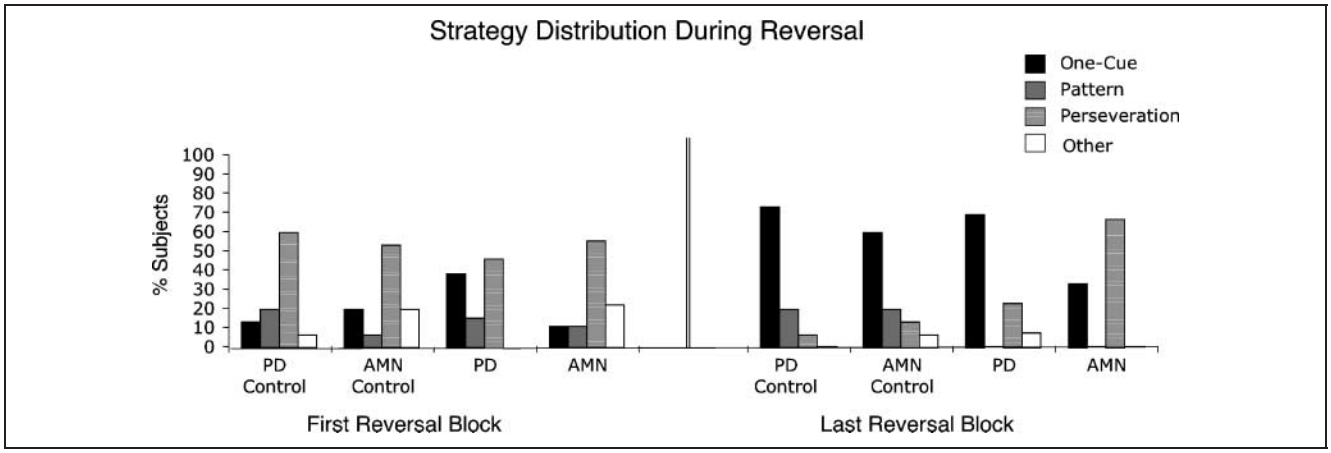


Figure 5. Distribution of individual subjects in each group according to model-based analyses of learning strategies during reversal. During the initial reversal block, a large proportion of subjects in all groups exhibited perseverative responding, making the same response to the same cue as during acquisition. By the last block of reversal, by contrast, most control and Parkinson subjects were responding with an appropriate ''one-cue'' strategy. Most amnesic subjects, by contrast, were still responding based on the same cue and response as during acquisition. PD = Parkinson; AMN = amnesics.

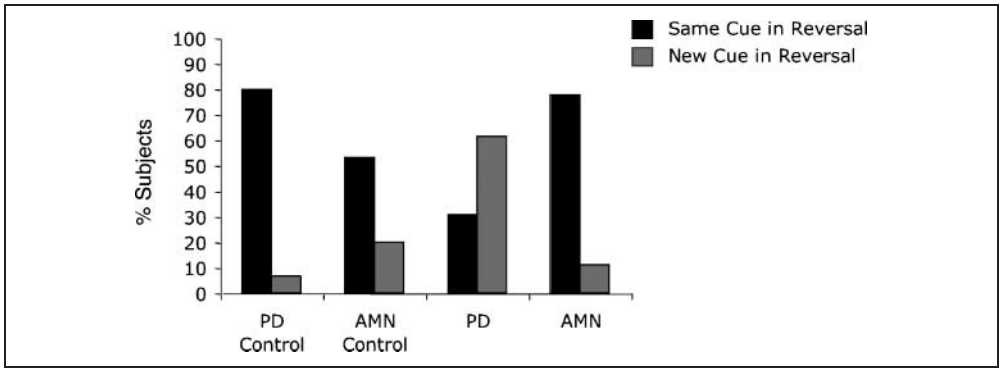


Figure 6. Distribution of individual subjects according to whether they used the same cue in reversal as in acquisition, or whether they learned to respond to a new cue in reversal. Parkinson patients showed a tendency to use a new cue during reversal, effectively ''opting out'' of the reversal by learning a new stimulus–outcome association. PD = Parkinson; AMN = amnesics.

Relation of Strategy to Behavior

Across all groups, there was a significant relationship between strategy and performance level in the final acquisition block [ANOVA on Acq Block 4 percent correct × Strategy (one cue, pattern, none), $F(2, 49) = 11.79$, $p < .001$]. Post hoc Tukey comparisons indicated this finding was due to significantly better performance among subjects fit by a pattern strategy versus the one-cue strategy, and better performance among those fit by a pattern or a one-cue strategy relative to those not fit by any strategy. A similar result was found in the reversal phase [ANOVA on Reversal Block 4 × strategy (one cue, pattern, perseverative, none), $F(3, 48) = 4.7$, $p < .01$]. Post hoc comparisons found this was related to better performance in subjects using the one-cue or the pattern strategy compared to the perseverative strategy.

Relation of Performance to Demographic and Neuropsychological Measures

We examined whether demographic or neuropsychological measures were related to performance and strategy use among the patient and control groups. We found no correlation between age or education and performance, either during acquisition or reversal, across or within each group ($r < .2$, $p > .1$ for all comparisons, uncorrected). Similarly, strategy in acquisition and in reversal was not found to be related to either age or education (ANOVA on Age or Education × Strategy, all $p > .2$).

We separately analyzed the relation between neuropsychological measures and performance in each of the control and patient populations. Among the patient groups, these analyses revealed no significant effects of either disease measures (among the Parkinson patients, years since disease onset or H–Y stage), nor of any of the obtained neuropsychological measures (all ps $> .2$). It is worth noting, however, that given the size of the samples, these null effects should be interpreted with caution.

Among the controls, there was a significant correlation between performance on the digit span and performance during the acquisition phase of the task ($r = .71$, $p < .05$), but not the reversal. By contrast, scores on the NAART (an estimate of verbal IQ) were correlated with performance on the reversal phase of the task ($r = .88$, $p < .005$), but were not significantly related to acquisition, nor to strategy use during acquisition or reversal.

DISCUSSION

The present study explored hippocampal and basal ganglia contributions to probabilistic learning and reversal. We found that patients with hippocampal or basal ganglia disruption were able to successfully acquire stimulus–response associations during learning, while both patient groups were impaired at reversal. The data further suggest distinct hippocampal and basal ganglia contributions to reversal learning. Amnesic subjects failed to reverse their response when the stimulus–outcome contingencies changed, and instead continued to respond to the stimuli using the same response they used during acquisition. Parkinson subjects, by contrast, although slow to recover from changes in the stimulus–outcome contingencies, were able to eventually significantly improve their performance during the reversal phase. In contrast to the controls, who tended to master the reversal phase simply by reversing their existing cue–outcome association, Parkinson patients tended to select a new cue during reversal, and to learn a new stimulus–response association based on the new cue. Thus, the amnesic subjects perseverated in their responding during the reversal, whereas Parkinson subjects ''opted out'' of the reversal.

The finding that amnesic subjects with hippocampal damage perseverate by maintaining their prior response following reversal is consistent with other findings in animals (Marston et al., 1993; Fagan & Olton, 1986; Berger & Orr, 1983; Zola & Mahut, 1973) and humans (Myers et al., 2000, 2006; Carrillo et al., 2001). The present results extend those findings and demonstrate that this effect also occurs with probabilistic associations. The present results further suggest that patients with hippocampal damage do not change their strategy following a reversal, nor do they shift to learning about a new stimulus. The fact that these subjects perseverate,

rather than just respond randomly, suggests that their poor performance during the reversal was not simply an effect of forgetting or fatigue.

Prior studies in animals and humans have also demonstrated a critical role for the basal ganglia in reversal learning (Frank & Claus, 2006; Schoenbaum & Setlow, 2003; Cools et al., 2002). The present results are consistent with these prior findings, showing that patients with Parkinson disease do not reverse a response to a previously learned stimulus–reward association. The present study extends prior data and demonstrates that when given the option to adapt to a new *stimulus*, instead of needing to adapt to a new *response*, Parkinson patients are able to recover from the reversal.

The Basal Ganglia and the MTL in Probabilistic Learning

In the present study, both amnesic and Parkinson subjects learned the initial associations. This contrasts with prior findings with a different probabilistic classification task (Hopkins et al., 2004; Shohamy, Myers, Grossman, et al., 2004; Shohamy, Myers, Onlaor, et al., 2004; Poldrack et al., 2001; Knowlton et al., 1996). In these prior studies, four visual cues were each separately associated with one of two outcomes, such that on each trial, one to three cues were presented, each with varying probabilities, and optimal learning involved integrating information across all four cues and across multiple trials to predict the correct response. Results from strategy analyses demonstrated that early in learning, healthy controls rely on nonoptimal, single-cue strategies. Later in learning, healthy controls shift to the optimal strategy that depends on integration of associations across cues and trials (Gluck et al., 2002). Patients with mild basal ganglia disruption are impaired later in learning, and rely on single-cue, nonoptimal strategies throughout (Shohamy, Myers, Onlaor, et al., 2004), whereas patients with selective hippocampus damage are impaired even early in learning and do not consistently rely on any single strategy (Hopkins et al., 2004).

In the present design, high levels of performance can be achieved by learning a single-cue outcome association. Indeed, we found that all groups tend to rely on single-cue learning rather than optimally learning about the pattern (which was 100% associated with the outcome). Although this is not the optimal strategy, it is an effective strategy for performing the task, in that it is relatively simple and yet can lead to relatively high 80% correct performance.

Interestingly, though, the current design does allow optimal performance to be reached if subjects learn to associate the configuration of cues with the correct outcome. This type of configural learning is thought to depend on rapid, pattern separated learning processes in the hippocampus (Bakker, Kirwan, Miller, & Stark, 2008; Leutgeb, Leutgeb, Moser, & Moser, 2007). Thus, this type of learning involves the ability to encode a pattern separately from other overlapping patterns—an ability that would support the optimal learning strategy in the current paradigm, as well as potentially the ability to reverse this strategy. Because most subjects in the present study used a single-cue strategy rather than a configural one, it remains unknown to what extent this aspect of the paradigm may have contributed to the deficit in the amnesics. However, it is worth pointing out that in contrast to other groups, no amnesics were fit by a pattern strategy, consistent with the role of the hippocampus in pattern separation and configural learning.

The finding of intact one-cue learning among our Parkinson subjects is consistent with prior findings, suggesting that Parkinson subjects are particularly impaired at learning that involves integration of information across multiple cues and trials (Filoteo, Maddox, Salmon, & Song, 2005; Shohamy, Myers, Onlaor, et al., 2004; Shin & Ivry, 2003). Notably, other studies have shown that Parkinson patients are often impaired when asked to learn a rule defined on a single stimulus dimension, in the presence of irrelevant dimensions (Filoteo et al., 2005; Maddox, Aparicio, Marchant, & Ivry, 2005; Ashby, Noble, Filoteo, Waldron, & Ell, 2003; Owen, Roberts, et al., 1993). The present findings are not inconsistent with this pattern, as in the present design, there are no irrelevant dimensions.

Open questions remain regarding the necessity of the MTL for probabilistic learning. In a complex four-cue probabilistic classification task, functional imaging studies show MTL contributions early during probabilistic learning. Similarly, early patient studies found that amnesic subjects of mixed etiology had intact learning early, but were impaired later in training (Knowlton et al., 1996; Knowlton, Squire, & Gluck, 1994). However, a more recent study, considering amnesic patients with selective bilateral hippocampal damage, found that such patients are impaired at four-cue probabilistic learning even early in training (Hopkins et al., 2004). Here, we found that individuals with hippocampal damage were able to acquire the associations, suggesting that probabilistic learning can be supported by areas outside the hippocampus and the MTL, at least when learning is based on a single highly predictive cue.

Basal Ganglia and Feedback

Converging evidence indicates that the basal ganglia play an important role in probabilistic learning by modifying responses based on response-contingent feedback (Frank, 2005; Frank et al., 2004; Shohamy, Myers, Grossman, et al., 2004; Poldrack & Packard, 2003; Poldrack et al., 2001; Schultz, 2000; Schultz, Dayan, & Montague, 1997; Owen, Beksinska, et al., 1993). We previously demonstrated in parallel patient and imaging studies that the basal

ganglia support learning that relies upon trial-by-trial feedback, but not learning by ''observation,'' without feedback (Shohamy, Myers, Grossman, et al., 2004). The present findings emphasize, however, that not *all* learning that involves feedback depends on the basal ganglia. Indeed, individuals with basal ganglia damage sometimes have spared performance on tasks that involve corrective feedback (Shohamy et al., 2006; Swainson et al., 2006; Shohamy, Myers, Grossman, Sage, & Gluck, 2005). Taken together, these findings suggest that a task may involve corrective feedback, and yet be amenable to learning by other strategies and systems that are not *dependent* on feedback processing. Future studies are necessary to determine, more specifically, the circumstances when feedback-based learning depends on the basal ganglia.

Dopaminergic Medication, Feedback, and Reversal Learning

Dopaminergic modulation is thought to play an important role in reversal learning. In Parkinson disease, patients are typically treated pharmacologically to enhance dopamine levels, which is highly effective in treating the motor impairments. The effects of dopaminergic medication on cognition and learning are varied, with reports of both beneficial and detrimental effects, depending on the cognitive processes involved (Cools et al., 2001, 2006; Shohamy et al., 2005, 2006; Frank et al., 2004; Cools, Barker, Sahakian, & Robbins, 2003; Swainson et al., 2000).

In reversal learning, the effect of dopaminergic medication has been reported to depend on whether learning is driven by positive versus negative reinforcement: Dopaminergic medication (particularly dopamine agonists) has been shown to impair performance when learning is driven by negative feedback; however, when reversal learning was driven by reward, dopaminergic medication had no effect.

In the present study, all Parkinson patients were tested while ''on'' dopaminergic medication, and the study was not designed to afford a direct comparison of learning from positive versus negative reinforcement. However, prior reported data suggest that medication effects are likely to have contributed to the performance of the Parkinson patients here. One hypothesis is that individual variability in learning from positive versus negative feedback may have interacted with patients' tendency to ''opt out'' of the reversal. Future studies will explore this possibility.

Basal Ganglia and Shifting

Parkinson subjects are impaired at shifting attention from one stimulus to another (Slabosz et al., 2006; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Cools et al., 2001; Owen, Beksinska, et al., 1993; Owen, Roberts, et al., 1993). Here, we found that Parkinson subjects respond to the reversal by shifting to a new stimulus *more so* than healthy controls. Although this finding on the surface may appear to be contradictory, there are several important differences between the cognitive demands in the present task compared with prior studies that explicitly examined attentional shift. Prior studies focused on the ability to shift to a previously irrelevant stimulus, an ability impaired in Parkinson subjects (Slabosz et al., 2006; Lewis et al., 2005; Cools et al., 2001; Owen, Beksinska, et al., 1993; Owen, Roberts, et al., 1993). By contrast, in the present study, all stimuli are equally relevant during acquisition and during reversal. Furthermore, similar to the present results, prior studies have also shown that Parkinson patients sometimes prefer to shift to a new stimulus (e.g., Owen, Roberts, et al., 1993).

Frontal Contributions to Reversal Learning in Parkinson Disease and in Amnesics

A wealth of data suggests that the prefrontal cortex plays an important role in a variety of so-called executive functions, including selection, inhibition, and flexibility—all cognitive processes that are likely to contribute to reversal learning. Indeed, anatomically, the prefrontal cortex is famously interconnected with the basal ganglia (Alexander, DeLong, & Strick, 1986), and is also highly interconnected with the MTL (Suzuki & Amaral, 2004; Goldman-Rakic, Selemon, & Schwartz, 1984). Consistent with this, Parkinson patients often display frontal executive impairments.

In the present study, we found that among healthy controls, performance on the digit span correlated with learning during the acquisition phase (but not the reversal), a finding consistent with recent reports that working memory correlates with dopamine levels in the striatum (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008). Interestingly, the amnesic patients also displayed mild frontal impairments on neuropsychological tests, suggesting that frontal impairments may have contributed to the amnesics' reversal learning impairments as well. Notably, however, animals with much more selective hippocampal lesions also show reversal learning deficits that are qualitatively similar to those reported here, suggesting that the deficit in amnesic patients is not likely to be explained entirely as a frontal pathology. Taken together, these data suggest that reversal learning may involve parallel, or interactive networks involving the prefrontal cortex, the MTL, and the basal ganglia.

Summary

On a simple probabilistic learning task, both the hippocampus and the basal ganglia are necessary for reversal learning, but contribute to performance in different ways.

When confronted with a reversal of previously learned stimulus–outcome associations, healthy controls learn to reverse the response to the stimulus. Damage to either the basal ganglia or the hippocampus affects the ability to perform such a reversal. Patients with basal ganglia dysfunction due to Parkinson disease solved the task by shifting to a new cue during the reversal, and learning a new cue–outcome association based on that new cue; in contrast, amnesic subjects with bilateral hippocampal damage perseverated in their responding to the old cue and were unable to master the reversal phase. These data emphasize an emerging theme in recent investigations of memory systems, that similar overall learning levels in patient populations can often mask important qualitative and representational differences in how the learning occurs.

Acknowledgments

This research was supported by grants from the National Institute of Health (R01 MH065406 to C. E. M., and R01 NS047434-02 to M. A. G.), and from the National Science Foundation (BCS-0223910 to M. A. G.). We thank John DeLuca, Leo Wolansky, Samporn On-Laor, Kindiya Geghman, and Vicash Dindwall for assistance with data collection. We would also like to thank two anonymous reviewers for insightful comments on an earlier draft.

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