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An evaluation of the concurrent discrimination task as a measure of habit learning: performance of amnesic subjects

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Abstract

Habit learning has been defined as an association between a stimulus and a response that develops slowly and automatically through repeated reinforcement. Concurrent discrimination (CD) learning, in which subjects learn to choose the rewarded objects in a series of pairs, is believed to be an example of habit learning in monkeys. Studies of human amnesic subjects, however, have produced equivocal results, revealing impaired or absent learning on the same CD tasks that monkeys with medial temporal-lobe (MTL) lesions learn normally. One possible explanation for impaired performance in human amnesic subjects is that, unlike monkeys, human subjects use explicit memory to solve CD problems. To test this hypothesis, we administered a 10-object pair CD learning task to two amnesic subjects, HM and PN, and normal control subjects (NCS). Both amnesic subjects have severe anterograde amnesia with little ability to form explicit memories. On the CD task, they demonstrated little or no learning and acquired no explicit knowledge of the task procedures or reward contingencies. In contrast, NCS learned the task quickly and easily using explicit memory strategies. These results suggest that CD tasks cannot be learned by habit in human subjects, and emphasize the discrepancies between the human and monkey literature on habit learning.

Keywords: HM; Amnesia; Medial temporal lobe; Hippocampus; Recognition memory

1. Introduction

Several theories of memory posit the existence of two dissociable memory systems: (1) MTL-dependent explicit memory, a conscious knowledge of facts and events, and (2) MTL-independent implicit memory, an unconscious memory for skills and procedures [9,38]. One such theory has been proposed by Mishkin [42,43], who emphasizes a dissociation between 'memory' (explicit) and 'habit,' which he defined as 'non-cognitive' learning 'founded not on knowledge or even on memories (in the sense of independent mental entities) but on automatic connections between a stimulus and a response' [42]. Like skill learning and procedural learning, habit learning is described as an unconscious mechanism that is adapted for slow or incremental learning and is independent of MTL structures. Mishkin proposed that the neostriatum is the neural substrate for the habit learning system [43].

The habit learning model is distinct from other types of implicit learning in that it is reminiscent of the automatic stimulus-response associations that characterize the behaviorist account of learning [58]. Tests that are thought to elicit habit learning present a stimulus-response association that can be learned gradually despite impaired explicit memory. For example, in a water maze task, rats with hippocampal lesions learned to associate a visual pattern with the location of a hidden platform [46]. Concurrent discrimination (CD) learning is viewed as a kind of habit learning in monkeys. In a 24 h intertrial interval (ITI) CD task, monkeys were shown 20 pairs of objects once each day; one object in each pair was consistently

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baited with a food reward. Monkeys with impaired explicit memory due to bilateral MTL lesions were able to learn over several days (at the same rate as control animals) to choose the baited object [34,51]. On multiple-repetition CD tasks, in which each stimulus pair is shown several times each day, monkeys with MTL lesions have been shown to learn normally by some researchers [49], but not by others [12,13,33,41,45,47,65].

Human amnesic subjects who have lesions in the MTL or diencephalon demonstrate normal learning on a number of tasks despite impaired explicit memory [6–8,18,26]. The preserved learning in amnesic subjects resembles habit learning in that it occurs unconsciously and automatically. Unlike monkeys, however, amnesic humans are impaired relative to NCS on a 24 h ITI CD task [60]. Amnesic patients also have demonstrated impaired learning on multiple-repetition CD tasks in which 6, 8, or 15 pairs of stimuli were repeatedly presented each day for several days [1,50,60].

The discrepant results between the monkey and human literature bring the habit learning model into question. Indeed, several authors have criticized the habit learning theory. Gaffan [21] proposed that monkeys learn concurrent discriminations not by habit but by object-reward associative memory. He suggests that the dissociation between impaired learning on declarative memory tasks, such as delayed non-matching to sample, but normal learning on CD tasks by MTL lesioned monkeys can be explained by differing demands on object identification in the two procedures. Further, Gaffan proposes that findings of impaired CD learning by humans and monkeys with striatal lesions [29,63] can also be explained by the reliance of visual associative memory on a corticostriatal output pathway.

In a recent review [64], Wise also questioned the proposal that the neostriatum subserves a habit memory system in humans and animals [43]. Citing a lack of conclusive evidence, he suggests that studies attempting to demonstrate learning impairments in monkeys with striatal lesions have ignored significant learning while emphasizing subtle deficits [4,14,63]. Evidence for habit learning deficits in humans has also been slight (see [64] for a review and discussion), with most evidence to date citing impaired performance by patients with Parkinson's and Huntington's diseases on such proposed habit tasks as mirror reading, rotary pursuit, Tower of Hanoi, and serial reaction time (however, see [29] for a report of preserved habit learning in amnesic subjects).

Given these criticisms, it is necessary to test further the habit learning model in humans, and to explain the discrepant results between the monkey and human data. One proposal that has been put forth to explain these results comes from Squire and colleagues [57]. They noted that although amnesic humans do not reach the same level of proficiency as NCS on CD tasks, they do demonstrate improvement over time [1,50,60]. Furthermore, they suggest that the extent of improvement may be related to the severity of the amnesia (however, even mildly amnesic patients have demonstrated CD impairments [23]). Based on this evidence, they suggest that amnesic subjects show impaired CD learning because unlike monkeys, humans learn CD tasks explicitly. They found that, for amnesic subjects and NCS, the extent of learning on an 8-pair CD task was correlated with the extent of explicit knowledge that the subjects had about the reward contingencies [60], suggesting that learning depended on the use of explicit strategies. If true, this model would predict that severely amnesic patients with little explicit memory capacity would be unable to learn a CD task.

In order to test the proposal that CD learning depends on explicit memory in humans [60], we administered a CD task to two amnesic patients and NCS. In Experiments 1 and 2, we tested the amnesic subject HM and NCS on two versions a 10-object pair CD learning task. HM's bilateral MTL resection resulted in a profound global amnesia that appears to be more severe than most other published cases of amnesia [54,56,59]. Because of the severity of HM's explicit memory deficit, any improvement in his performance on the CD task would be evidence of habit learning. In contrast, if HM were unable to learn, this finding would support the proposal that CD learning depends on explicit memory in humans [57]. In Experiment 3, a second amnesic subject, PN, was also tested. PN exhibited explicit memory impairments comparable to HM's. Therefore, we reasoned that any learning that PN was able to achieve would be a result of habit learning.

2. Experiment 1

A pilot study in our laboratory of an 11-day CD task revealed no learning in HM. The pilot study followed similar procedures as those described below, but did not control for potential baseline preferences for certain objects, and thus it is not reported. Experiment 1 tested the hypothesis that globally amnesic human subjects can learn a CD task. A positive result would provide further evidence for the existence of a habit learning system in humans.

2.1. Methods

2.1.1. Subjects

HM and six NCS (two women) participated in this experiment. HM underwent a bilateral MTL excision

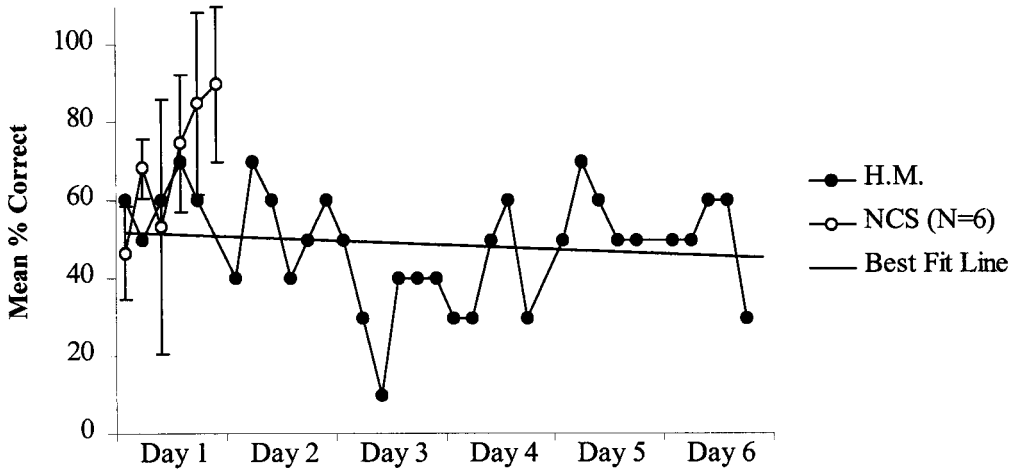

Fig. 1. Performance of HM and normal control subjects (NCS) on a 10-pair concurrent discrimination task (Experiment 1). The vertical bars represent the standard deviation for NCS. The best fit line was calculated from a linear regression analysis on HM's score (percentage of objects chosen correctly out of 10) for each trial. Chance performance is 50%.

in 1953 in an attempt to alleviate severe epileptic seizures [56]. Since that time, he has demonstrated a profound anterograde amnesia, which has been documented previously [10,11,40]. At the time of testing, HM was 69 years of age with an educational level of 12 years. His Wechsler Adult Intelligence Scale-Revised (WAIS-R) Full Scale, Wechsler Memory Scale-Revised (WMS-R) General, and WMS-R Delayed Recall Scores were 94, 87, and 55 respectively[1]. NCS had a mean age of 69.3 ± 3.1 years and a mean educational level of 12.0 ± 0.0 years (all descriptive statistics are given as mean $\pm$ SD). NCS had normal neurological examinations and no history of neurological or psychiatric disease.

2.1.2. Stimulus materials and apparatus

Twenty objects were randomly divided into 10 pairs (sponge/toy boat; ribbon/date stamp; eraser/comb; six-sided die/spool of thread; spoon/Scotch tape; scissors/key; toothbrush/electrical plug; candle/pen; paper clip/light bulb; can opener/film case). The objects were chosen to be representative examples of everyday 'junk objects', similar to those used in monkey CD tasks [42]. Each object was mounted onto an opaque plastic box that was used to conceal a dime reward underneath the target object of each pair. The test was administered in a simulated Wisconsin General Testing Apparatus (WGTA), which consisted of a wooden frame with a curtain that could be raised or lowered to reveal the objects to the subject.

2.1.3. Procedure

Each trial began when the experimenter raised the curtain to reveal a pair of objects to the subject. One object in each pair was designated the 'target,' as described below. On each trial, a dime reward was concealed under the plastic box holding the target object. Subjects were told that a dime was hidden underneath one of the objects, and that they should try to win as many dimes as possible (the instructions were repeated to HM before each testing block). They pointed to the object they thought was correct, and that object was lifted by the experimenter. If correct, the subject retrieved the dime. The experimenter corrected incorrect choices by briefly displacing the target object to reveal the dime.

To control for baseline preferences in HM, the target object of each pair was determined in a pretest block of 10 trials on the first day, in which the object not chosen in each pair became the rewarded item for the duration of testing. This pretest block occurred 1 h before the first CD trial; HM was told that one object of each pair was 'correct', and that if he chose the correct object he would be given a dime. Because each chosen object was subsequently designated as incorrect, HM was told that he had chosen incorrectly on each trial. For NCS, no pretest block was given, instead, the target object was randomly determined for each subject before CD testing began.

Objects were presented in six blocks (each consisting of 10 trials) per day, each block was separated by 1–2 h. HM was tested for six consecutive days; NCS were tested for one day. The left/right position of the target on each trial varied pseudorandomly [25]; targets appeared in both positions an equal number of times. Object pairs appeared in a different randomly determined order in each block.

[1] Comparison of HM's performance on the WAIS-R, the Wechsler Adult Intelligence Scale, and the Wechsler Bellevue Scales I and II reveal that his IQ scores have not changed significantly since his initial postoperative evaluation

HM was asked to state his response strategy at the end of each testing block. NCS were given no formal assessment of explicit knowledge because their comments clearly indicated that they were relying on conscious recollection.

2.2. Results

A linear regression analysis of HM's scores over all 6 days showed that the slope of the best fit line computed for his performance across blocks was not significantly different from zero ($P > 0.4$), indicating that his performance did not differ significantly from chance. HM's mean percentage correct (across blocks) was $60.0\% \pm 7.1\%$ for Day 1 and $50.0\% \pm 12.2\%$ for Day 6. In contrast, on the NCS's single testing day, they achieved a mean percentage correct of $46.7\% \pm 12.1\%$ for Block 1 and $90.0\% \pm 20.0\%$ for Block 6 (Fig. 1). A linear regression analysis indicated that this increase was significant, that is, the slope of the best fit line computed for the NCS single day block means was significantly different than zero ($P < 0.02$).

Comments made by all NCS indicated that they were aware by the end of Day 1 that the same object in each pair was always rewarded. In contrast, HM had no explicit knowledge of the reward contingencies at any time. When asked to state his response strategy at the end of each block, his most common response was that he simply picked the object on the opposite side (right or left) each time. Other strategies included choosing the most useful object, choosing the object he would most like to own, and simply guessing. HM's performance did not seem to be affected by any baseline object preferences, as indicated by his near-chance performance on the first CD block after the pretest block. Further, because of the 1 h delay between the pretest and the first CD block, HM could not have used short-term memory to recall his choice on the pretest. Rather, his responses seemed to be dependent on one of the several strategies noted above.

2.3. Discussion

After six days of testing, HM demonstrated no improvement in his ability to choose the rewarded object. Thus, with no explicit knowledge of the reward contingencies, HM was unable to learn. Although NCS were tested for only one day, they achieved a significant increase in performance over the six testing blocks, demonstrating a clear trend toward perfect performance. This result lends support to the proposal that CD learning depends on explicit memory in humans [57]. Possible alternate interpretations will be discussed later.

3. Experiment 2

A strict interpretation of the habit learning model [42,43] predicts that reinforcement increases the probability that a certain *motor* response will occur. Tests of CD learning in monkeys and rats typically require the animal to reach for or move to target objects, in order to facilitate an association between the approach response and the rewarded stimulus. Although we found no evidence of learning by HM in Experiment 1, our procedure was not designed to elicit stimulus-*motor* response associations. To determine whether an approach response is necessary for habit learning to occur, Experiment 2 added a motor approach response to the procedure of Experiment 1. In addition, Experiment 2 lengthened the time of testing for NCS to four consecutive days, in order to confirm that NCS learn the CD task quickly and completely.

3.1. Methods

3.1.1. Subjects

Five new NCS (three women) and HM were tested. HM was 69 years old. NCS had a mean age of 69.0 ± 2.2 years and a mean educational level of 12.0 ± 0.0 years.

3.1.2. Procedure

Experiment 2 took place four months after Experiment 1. The same modified WGTA and object pairs were used[2]. The procedures were identical to those of Experiment 1 with the following exceptions: (1) rather than pointing, subjects were required to reach for and displace the object they thought was correct (similar to the method by which monkeys reach for and displace objects in CD and delayed nonmatching to sample tasks using the WGTA); this reach response was stressed in the instructions and was demonstrated by the experimenter (for HM, the instructions and demonstration were repeated before each testing block); (2) NCS were tested for four consecutive days; HM was tested for six consecutive days; (3) to control for baseline preferences in HM and NCS, the target object of each pair was determined in a pretest trial on the first day; the object not chosen became the rewarded item for the duration of testing (the same procedure that was used for HM in Experiment 1).

[2] Previous experience in our laboratory indicates that HM remembers nothing about testing sessions from visit to visit, therefore we had no concerns about transfer of learning between experiments.

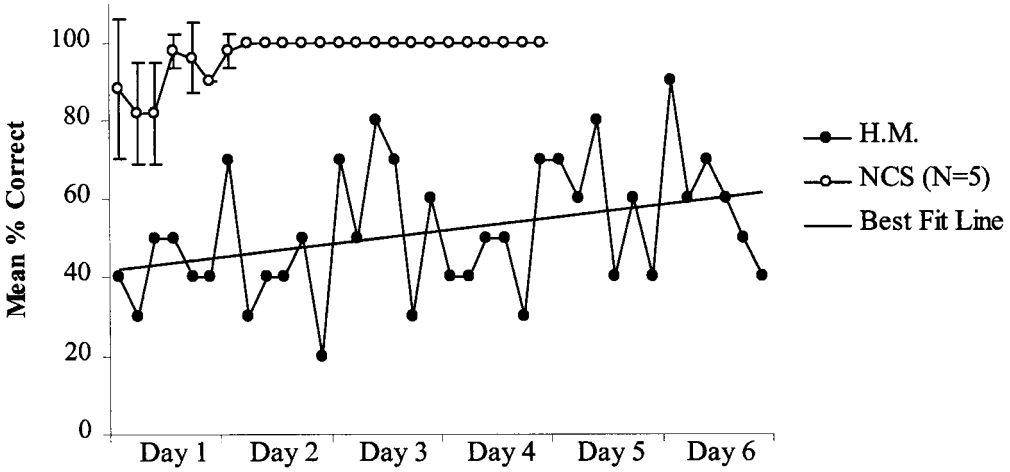

Fig. 2. Performance of HM and normal control subjects (NCS) on a 10-pair concurrent discrimination task (Experiment 2). The vertical bars represent the standard deviation for NCS. The best fit line was calculated from a linear regression analysis on HM's score (percentage of objects chosen correctly out of 10) for each trial. Chance performance is 50%.

3.2. Results

Mann–Whitney tests indicated that HM's mean percentage correct across blocks over all six days (51.7% ± 16.6%; number of observations = 36 blocks) was significantly lower than each NCS's mean percentage correct across blocks over all four days (100% ± 0.0%, 94.2% ± 11.0%, 98.7% ± 4.6%, 97.9% ± 5.1%, 94.5% ± 12.3% for subjects 1–5, respectively; mean number of observations = 22 blocks; $P < 0.001$ for each of the five independent Mann–Whitney tests). All NCS learned the task to 100% ± 0.0% accuracy within the four days of testing, improving from a mean of 88.1% ± 13.2% correct on Day 1 to a mean of 100% ± 0.0% correct on Day 4 (asymptotic perfect performance was reached by three subjects in five blocks and by all subjects in eight blocks).

A linear regression analysis revealed that the slope of the best fit line computed for HM's performance across blocks was significantly greater than zero ($P < 0.04$), increasing from a mean percentage correct of 41.7% ± 7.5% on Day 1 to 61.7% ± 17.2% on Day 6 (Fig. 2). This result indicated that, despite overall poorer performance relative to control subjects, HM's performance did improve significantly over time.

Although explicit knowledge was not formally tested for NCS, it was clear by the end of Day 1 that all NCS were aware that the same object in each pair was rewarded consistently; upon choosing incorrect objects, NCS frequently made comments to the effect of having forgotten which object had been rewarded before. In contrast, HM had no explicit knowledge of the reward contingencies at any point during testing. When asked to state his strategy at the end of each testing block, HM's most common responses were similar to those stated in Experiment 1 (i.e., choosing the opposite side each time, choosing the most useful object, and guessing).

3.3. Discussion

Although HM's performance was impaired relative to that of NCS, he did demonstrate a slight but statistically significant improvement in his ability to choose the rewarded object. Because HM had no explicit knowledge of the reward contingencies, his learning could only have occurred implicitly, and may have been an example of habit learning. These results suggest that including an approach response in the test paradigm may be necessary to elicit habit learning in a subject with no explicit memory. However, given the discrepant results of Experiments 1 and 2, and the marginally significant effect in Experiment 2, a third CD experiment (Experiment 3) was conducted in order to provide a more comprehensive investigation of habit learning in amnesia.

4. Experiment 3

Experiment 3 was designed to replicate the results of Experiment 2 with HM and a second amnesic subject, PN. In addition, tests of explicit memory and object recognition were given to clarify the extent of the subjects' explicit knowledge of the test stimuli and procedures.

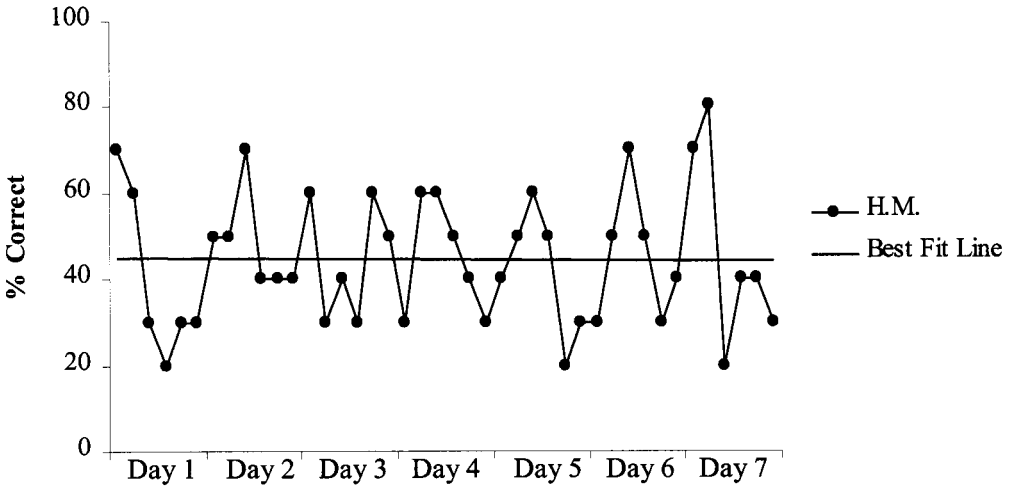

Fig. 3. Performance of HM on a 10-pair concurrent discrimination task (Experiment. 3). The best fit line was calculated from a linear regression analysis on HM's score (percentage of objects chosen correctly out of 10) for each trial. Chance performance is 50%.

4.1. Methods

4.1.1. Subjects

HM was 70 years old at the time of testing with WAIS-R Full Scale, WMS-R General, and WMS-R Delayed Recall Scores of 99, 74, and 54, respectively. The second amnesic subject was PN, a 62-year-old woman with profound anterograde amnesia and bilateral MTL damage due to herpes simplex encephalitis at age 58 years and a hypoxic episode at age 60 years. PN's lesion consisted of abnormalities in the hippocampal formation, parahippocampal gyri, and perirhinal cortex bilaterally. She had 16 years of education, and her WAIS-R Full Scale, WMS-R General, and WMS-R Delayed Recall Scores were 124, 77, and 50, respectively. In our laboratory, PN exhibits a degree of anterograde amnesia comparable to that observed in HM No NCS were tested in this experiment.

4.1.2. Procedure

Experiment 3 took place six months after Experiment 2. The same modified WGTA and object pairs were used. The procedures were identical to those of Experiment 2 with the following exceptions: (1) HM was tested over seven consecutive days and PN was tested for six consecutive days; (2) tests of explicit memory and object recognition were given in addition to the CD procedure (described below); (3) the instructions were modified slightly during the course of the experiment due to a response strategy noted in HM, described below.

4.1.3. Explicit knowledge assessment

Before each CD testing block, HM and PN were asked a series of questions to assess their explicit knowledge of the test. First, they were asked whether they had seen the apparatus before, and if so when and how many times. Second, they were asked (with the curtain lowered) what was behind the curtain and what the goal of the task was. Third, they were presented with the container used to store the dimes they would receive as rewards, and were asked what its purpose was. After each block of CD testing, subjects were asked to state how they decided which object to choose in each pair.

4.1.4. Object recognition test

Both subjects were given a two-object forced-choice recognition task. This task was given once at least 1 h before CD testing began (in order to assess baseline performance), and again 1 h after the completion of CD testing. For this task, the experimenter raised the curtain of the modified WGTA to present a pair of objects, consisting of one object used in the CD test and one foil object that the subject had not seen during CD testing. Thus, every test object was presented once in each administration of the recognition task, along with its corresponding novel foil. Each foil object was the same as the CD test object with which it was paired, but the foils differed in one or two attributes. For example, a red toothbrush was presented with a green toothbrush, and a pink rectangular sponge was presented with a blue oval sponge. Subjects were told that they had taken a test in which they had seen one object in each pair, and that they should point to the one they remembered seeing before, and to guess if they did not know. The same foil objects were used on each administration of the object recognition task, but the object pairs were presented in a different random order each time. Left/right presentation of the CD test object varied pseudorandomly [25]. Subjects were not given any feedback

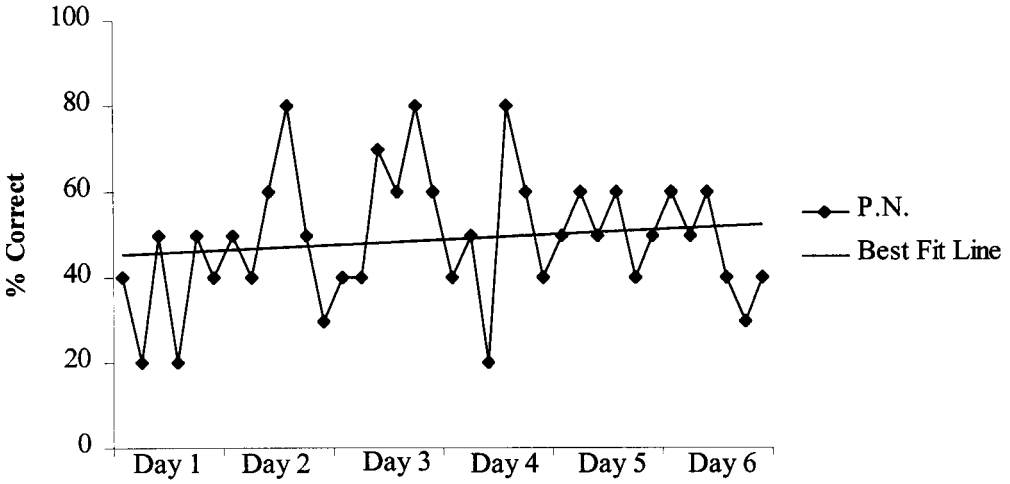

Fig. 4. Performance of PN on a 10-pair concurrent discrimination task (Experiment 3). The best fit line was calculated from a linear regression analysis on PN's score (percentage of objects chosen correctly out of 10) for each trial. Chance performance is 50%.

about their performance either during or after the recognition test sessions.

4.1.5. Results

A linear regression analysis of HM's scores over seven days showed that the slope of the best fit line computed for his performance across blocks was not significantly different than zero ($P > 0.90$), indicating that his performance did not differ significantly from chance (Fig. 3). HM achieved a mean of $40.0\% \pm 20.0\%$ correct on his first testing day and a mean of $46.7\% \pm 23.4\%$ correct on his last.

A linear regression analysis for PN's scores over six days showed that the slope of the best fit line computed for her performance across blocks was not significantly different than zero ($P > 0.40$), indicating that her performance also did not differ significantly from chance (Fig. 4). PN achieved a mean of $36.7\% \pm 13.6\%$ correct on her first testing day and a mean of $46.7\% \pm 12.1\%$ correct on her last.

4.1.6. Pre-test explicit knowledge assessment

Qualitative assessment of the subjects' performance on the questions of explicit memory given to them before each CD session indicated that they had no explicit knowledge of the test procedures or reward contingencies at any time. HM's description of the procedure was most nearly correct on Day 1, before any CD testing had begun (six months after his previous exposure to the test in Experiment 2), thus indicating that he was probably guessing. On subsequent occasions, after many CD sessions, his responses revealed no memory of the nature of the task or of the

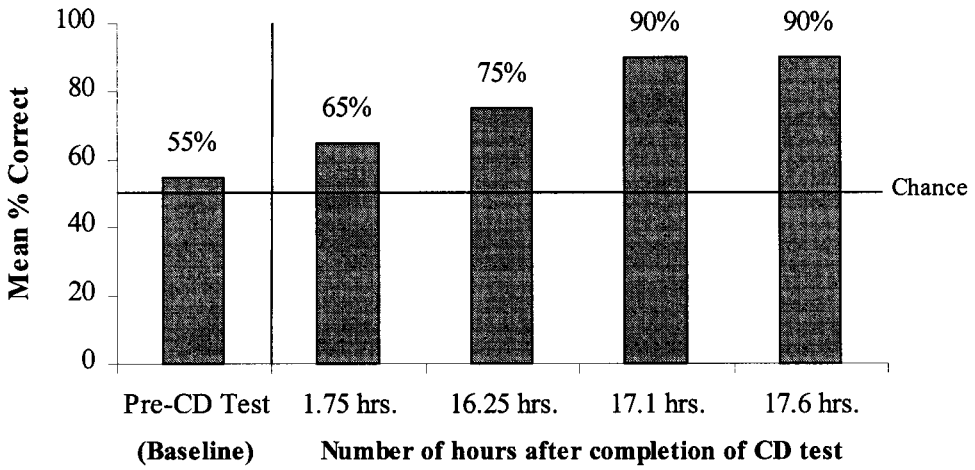

Fig. 5. Object recognition memory performance for HM. The Pre-CD Test data gives HM's baseline performance on the recognition task 17 h before CD testing began. Object recognition tests were then given 1.75, 16.25, 17.1, and 17.6 h after completion of the final CD session. Percentage correct scores (number of test objects correctly identified out of 20 pairs) are given above each bar. Chance performance (50%) is indicated by a horizontal line.

stimuli. Similar results were obtained from PN; after many exposures to the CD test, she had no recollection of having taken it before nor could she describe the objects or state the reward contingencies.

4.1.7. Object recognition assessment

We administered five object recognition assessments to HM. In the first session (baseline assessment), which occurred 17 h before the start of CD testing, HM correctly identified 55% of the CD test objects. One hour after completion of the last CD test session on Day 7, the object recognition task was repeated, and HM correctly identified 65% of the CD test objects. In order to determine the reliability of this result, the task was repeated 3 more times 16 h later, with 30–45 min of distraction between each administration. In these three final sessions, HM correctly identified 75, 90, and 90% of the CD test objects, respectively (Fig. 5). In contrast to HM's apparently good recognition memory for the CD test objects, PN performed at chance levels (50%) on the object recognition task, both 1 h before and 1 h after CD testing (due to time constraints, we were unable to repeat object recognition testing with PN as was done with HM).

4.1.8. Post-test explicit knowledge assessment

By the third day of testing, it became clear that HM was using a single response strategy: choosing the 'most useful' object. Because this strategy could have interfered with any habit learning of the reward contingencies, we changed the instructions slightly on subsequent sessions. Specifically, we encouraged him to use his 'gut feeling' to help him decide which object to choose, rather than relying on any one particular strategy. Despite frequent repetition of this instruction, HM continued to choose what he considered the 'most useful' object for most testing blocks, although his assessment of which object was most useful was inconsistent across blocks. The same instructions were also given to PN, who did not exhibit any consistent response strategy.

4.1.9. Discussion

In contrast to the results of Experiment 2, and in agreement with the results of Experiment 1, HM demonstrated no learning on a CD task over seven days. A second amnesic subject, PN, also failed to learn the CD task over 6 days. Thus, with no access to explicit knowledge of the task or the reward contingencies, HM and PN were unable to learn. This result is consistent with the hypothesis that CD learning depends on explicit memory, rather than habit memory, in humans [57,60]. We will, however, discuss alternative explanations below.

It is possible that HM's reliance on a single response strategy, choosing the most useful object, might have obscured any habit learning that took place: frontal lobe dysfunction, rather than memory impairment, might have interfered with the expression of CD learning. Previous studies in our laboratory, however, have not suggested any contamination by perseverative strategies in learning tasks, or any other evidence of such frontal-lobe dysfunction in HM. For example, on an administration of the Wisconsin Card Sorting Test [27,39] near the time of CD testing, HM performed normally and obtained a normal number of perseverative errors. In addition, HM failed to learn on Experiment 1, in which he demonstrated a wider range of response strategies. Thus, HM's failure to learn on Experiment 3 cannot be explained by his use of a single response strategy.

HM's remarkably good recognition memory for the test objects, coupled with a complete lack of implicit or explicit learning on the CD task, was surprising. HM received no feedback about his performance on any of the object recognition sessions. Thus, his improvement in performance after several administrations of the task cannot be attributed to learning during the object recognition sessions. HM's good recognition memory for the CD objects is reminiscent of his performance on a test of picture recognition memory, in which he was able to identify previously viewed complex colored magazine pictures after delay intervals of up to six months [16,17]. Aggleton and Shaw [2] have proposed that amnesic subjects with discrete lesions in the hippocampus, fornix, or mammillary body achieve better performance on a recognition memory test than amnesic subjects with widespread MTL damage, despite comparable levels of anterograde amnesia (but see [53]). This result suggests that recognition memory could be at least partially spared, even in the case of severe anterograde amnesia.

Studies in monkeys have identified area TE (in the anterior middle and inferior temporal gyri) and the perirhinal cortex (part of the inferior temporal gyrus) as being required for recognition memory [19,36,44,48]. In addition, electrophysiological studies in monkeys demonstrate decreased activity of neurons in the perirhinal cortex and lateral TE during exposure to familiar stimuli [3,32,37,55]. Recent anatomical MRI images of HM's brain reveal sparing in the ventrocaudal perirhinal cortex and lateral middle and inferior temporal gyri [11]. Moreover, in humans the lingual and fusiform gyri (which are also preserved in HM) have been shown to subserve novel picture encoding [61]. Thus, neurons in these areas may provide a familiarity effect that HM could use to make recognition judgments. In addition, studies have demonstrated that the perirhinal cortex is not involved in concurrent discrimination learning [22], suggesting that sparing in this area could provide HM with some

recognition memory ability, without assisting in CD learning. Lesions to area TE have been shown to result in CD learning impairments [5,24], although monkeys with TE lesions are eventually able to learn the CD problems. Thus, area TE may also support some recognition memory ability, without being sufficient for normal CD learning. Although it is unclear whether these areas that appear intact in MRI images of HM's brain could support normal function, unpublished results from our laboratory demonstrate significant fMRI activation in HM's spared left parahippocampal gyrus during picture encoding. Thus, spared function in these cortical areas may provide HM with some recognition memory ability. It is important to note, however, that Squire and colleagues have reported that preserved recognition memory in amnesic subjects may be dependent on spared MTL function, rather than on familiarity responses mediated by area TE [52].

In contrast to HM's good recognition memory, PN performed only at chance on the recognition test. Differences between the etiology and extent of temporal-lobe damage in the two patients may account for this discrepancy in recognition memory [52]. However, we do not have sufficiently detailed anatomical information about the exact locus and extent of PN's lesion to speculate on the specific differences that could explain her recognition memory impairment.

5. General conclusions

Three tests of CD learning in the amnesic subject HM revealed equivocal results: no learning on two occasions, and slight but statistically significant learning on a third occasion. Overall, HM did not demonstrate reliably significant CD learning. Similarly, a second amnesic subject, PN, did not demonstrate any learning on the same CD test. Although results from CD tasks have often been used to provide support for models of a MTL-independent habit learning system in humans [1,28,50,60,62] and animals [33,34,47,51,65,66], our results reveal impaired performance by amnesic humans on a task that monkeys with MTL lesions learn normally.

We have considered four possible explanations for the discrepancy between the performance of our amnesic subjects and the performance of monkeys with MTL lesions on CD tasks. The first, which was proposed by Squire and colleagues [57], is that CD learning cannot be learned by habit in human subjects but instead depends on explicit memory. Thus, while monkeys with impaired explicit memory are able to learn concurrent discriminations, possibly by habit [42,43], humans are for some reason unable to learn the task other than by explicit memorization of the reward contingencies. If this view is correct, then we must ask why human subjects would be dependent on explicit memory for CD learning when the monkey is not. One possibility is that during the course of evolution, humans have lost a memory mechanism that still exists in the monkey. By this reasoning, lesioned and normal monkeys could use a habit system to solve CD problems, performing better than amnesic humans, who have no habit system and a non-functioning explicit memory system. Our amnesic subjects were unable to exceed chance performance in either 360 trials (in Experiments 1 and 2) or 420 trials (in Experiment 30), whereas in 20-pair, 24 h. ITI CD tasks, normal and lesioned monkeys have been shown to reach a criterion performance of 90% correct in less than 300 trials [34,35,51]. Thus, the loss of a habit mechanism in humans could account for the present results; however, this explanation seems unlikely.

A second possibility is that humans, with more advanced problem solving skills, use their faster, more efficient explicit memory system to attempt to solve CD problems. This reasoning leads to the prediction that the absence of explicit memory in human subjects would permit the (intact) habit learning system to acquire CD information. Thus, human amnesic subjects should perform as well as monkeys with MTL lesions, who also rely on habit to solve CD problems. Our data do not support this argument. However, our data would be consistent with this explanation if one assumes that the recruitment of explicit memory by humans to solve the CD task is a strategic choice. According to this view, conscious attempts by the human amnesic subjects to use explicit memory would interfere with the expression of correctly formed habits. This suggestion predicts that CD tasks could be learned by habit in amnesic humans, but that expression of the habit response (which is by definition unconscious) is blocked by a conflicting conscious strategy. For example, as we mentioned previously (Experiment 3, Results), by the third day of testing, it became apparent that HM was primarily using a single response strategy, i.e., choosing 'the most useful object.' It is possible that his attempts to apply a strategy to the problem prompted him to choose against an unconscious inclination provided by a habit system. Nevertheless, HM did not perform consistently better on blocks for which he did not report a strategy, and PN, who had no consistent strategy other than pure guessing, was also unable to learn the task.

A third potential explanation for the impaired performance of our amnesic subjects is that the CD task used in the present study was not the same procedurally as the CD tasks that monkeys with MTL lesions learn normally. In the monkey literature, the 20-pair, 24 h ITI CD task has revealed different results compared to an 8- or 10-pair, multiple-repetition CD task like the one used in the present study. Monkeys with

MTL lesions typically perform normally on 24 h ITI tasks [34,51], but many groups have found them to be impaired on multiple-repetition CD tasks [12,13,33,41,45,47,65]. When compared to monkeys given multiple-repetition CD tasks, the performance of our amnesic subjects more closely matches that of lesioned monkeys. In three studies [33,47,65], normal monkeys reached a criterion of 97.5% correct in a mean of 330, 456, and 530 trials, respectively, whereas monkeys with MTL lesions required a mean of 902, 1426, and 1100 trials. The discrepant results between these two forms of the task could be explained if humans and monkeys have both habit and explicit memory systems, but the habit system is activated only when the task exceeds the capacity of the normally functioning explicit memory system. In monkeys, the numerous object pairs and long retention interval in the 24 h ITI task may exceed the capacity of the explicit memory system, forcing both groups to rely on habit, and producing comparable results in lesioned and control animals. In humans, artificial grammar learning [30] and probabilistic classification learning [29,31] are other examples of tasks that cannot be learned explicitly by normal subjects, and elicit normal performance in amnesic subjects, possibly because both groups use habit memory to solve the task. The present results, therefore, can be explained if the 10-pair multiple-repetition CD task can be learned explicitly by normal monkeys and humans, but only by habit by lesioned monkeys and amnesic humans. Because the habit system requires a longer time to form stimulus-response associations, the performance of amnesic groups is impaired relative to control groups. By this view, we would expect that our amnesic humans should be able to use a habit system to match the performance of monkeys with MTL lesions if given a comparable number of trials. However, Squire and colleagues administered a CD task to amnesic humans for 20 days and found no significant learning [60]. Alternately, had we administered a version of the CD task with an ITI of several weeks or months, we might have exceeded the explicit memory capacity of healthy control subjects, and thus produced normal performance in amnesic humans by forcing both groups to rely on habit. Because these experiments were not performed this argument is speculative. In addition, recent evidence suggests that the impairments observed in monkeys with MTL lesions on multiple-repetition CD tasks can be explained entirely by inadvertent damage to area TE [5], rather than by differential memory requirements.

Another procedural difference between the CD task as it is administered to monkeys and humans has been noted by Gaffan [20]. He suggested that because human subjects have seen the CD objects outside of the experimental situation, they must discriminate between the experimental context and previous encounters in order to form a new association between the object and its associated reward. In contrast, monkeys presumably would not have seen the objects before, and thus would not need to recall contextual information. Because the MTL system is required for the memory of contextual cues, it might follow that human amnesic subjects would be impaired on CD tasks employing common 'junk' objects, whereas monkeys with MTL lesions would perform normally [20]. Evidence for this view comes from Murray and colleagues [15] who reported that monkeys with MTL lesions are impaired on CD tasks when they must discriminate objects in different contexts. Thus, if monkeys are required to recall contextual information about the objects used in CD tasks, contextual associations mediated by the explicit memory system would become important, and animals with MTL lesions would be impaired on the task. This suggestion is similar to Squire's proposal that humans require explicit memory to solve CD tasks [57], and offers an explanation for the discrepancy between monkey and human results that exists both in the literature and in the present results.

A fourth explanation for the observed results is that the MTL lesions in the monkey studies do not correspond to the lesions in our human amnesic subjects. As was mentioned previously, cortical areas outside of the hippocampus, such as area TE [5,24], have been shown to subserve CD learning. Thus, unnoticed or unintentional damage either in the amnesic subjects or in the lesioned monkeys could account for the widespread discrepancies in the literature. This final possibility is especially important because in this case one of the amnesic subjects is HM, whose lesion researchers have been trying to replicate in the monkey for decades. However, a recent re-analysis of HM's lesion [11] suggests that the extent of damage is less than previously thought. Therefore, the monkey lesion studies, which attempted to replicate the original surgical reports of HM's lesion [56], might have actually overestimated the extent of damage. If so, we would expect monkeys with MTL lesions to perform worse than HM, which is again inconsistent with our results.

Our results emphasize the discrepancies between monkey and human data that have characterized studies of CD learning and habit memory. Although we are unable to arrive at an unequivocal theoretical interpretation for our data, one conclusion from this study is clear: CD tasks, as they are typically administered, fail as a measure of habit learning in humans. The controversy over whether humans and monkeys share a neostriatal habit memory system remains unresolved. However, the present results confirm that, despite attempts to create complementary test pro-

cedures and lesions between humans and monkeys, CD tasks will not be appropriate to resolve the issue.

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References

[1] Aggleton JP, Nicol RM, Huston AE, Fairbairn AF. The performance of amnesic subjects on tests of experimental amnesia in animals: Delayed matching-to-sample and concurrent learning. Neuropsychologia 1988;26:265–72.
[2] Aggleton JP, Shaw C. Amnesia and recognition memory: A reanalysis of psychometric data. Neuropsychologia 1996;34:51–62.
[3] Brown MW, Wilson FAW, Riches IP. Neuronal evidence that inferotemporal cortex is more important than hippocampus in certain processes underlying recognition memory. Brain Research 1987;409:158–62.
[4] Buerger AA, Gross CG, Rocha-Miranda CE. Effects of ventral putamen lesions on discrimination learning by monkeys. Journal of Comparative and Physiological Psychology 1974;86:440–6.
[5] Buffalo EA, Stefanacci L, Squire LR, Zola SM. A reexamination of the concurrent discrimination learning task: the importance of anterior inferotemporal cortex, area TE. Behavioral Neuroscience 1998;112:3–14.
[6] Cohen NJ, Corkin S. The amnesic patient, HM: Learning and retention of a cognitive skill. Society for Neuroscience Abstracts 1981;7:235.
[7] Cohen NJ, Squire LR. Preserved learning and retention of pattern-analyzing skill in amnesia: Dissociation of knowing how and knowing that. Science 1980;210:207–10.
[8] Corkin S. Tactually guided maze-learning in man: Effects of unilateral cortical excisions and bilateral hippocampal lesions. Neuropsychologia 1965;3:339–51.
[9] Corkin S. Acquisition of motor skill after bilateral medial temporal lobe excision. Neuropsychologia 1968;6:225–65.
[10] Corkin S. Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in HM. Seminars in Neurology 1984;4:249–59.
[11] Corkin S, Amaral DG, Johnson KA, Hyman BT. HM's medial temporal-lobe lesion: Findings from MRI. Journal of Neuroscience 1997;17:3964–79.
[12] Correll RE, Scoville WB. Effects of medial temporal lesions on visual discrimination performance. Journal of Comparative and Physiological Psychology 1965;60:175–81.
[13] Correll RE, Scoville WB. Relationship of ITI to acquisition of serial visual discriminations following temporal rhinencephalic resection in monkeys. Journal of Comparative and Physiological Psychology 1970;70:464–9.
[14] Divac I, Rosvold HE, Szwarcbart MK. Behavioral effects of selective ablation of the caudate nucleus. Journal of Comparative and Physiological Psychology 1967;63:184–90.
[15] Dore FY, Thornton JA, White NM, Murray EA. Selective hippocampal lesions yield nonspatial memory impairments in rhesus monkeys. Hippocampus 1998;8:323–9.
[16] Freed D, Corkin S. Rate of forgetting in HM: 6-month recognition. Behavioral Neuroscience 1988;102:823–7.
[17] Freed D, Corkin S, Cohen N. Forgetting in HM: A second look. Neuropsychologia 1987;25:461–71.
[18] Gabrieli JD, Corkin S, Mickel SF, Growdon JH. Intact acquisition and long-term retention of mirror-tracing skill in Alzheimer's disease and in global amnesia. Behavioral Neuroscience 1993;107:899–910.
[19] Gaffan D. Dissociated effects of perirhinal cortex ablation, fornix transection and amygdalectomy: evidence for multiple memory systems in the primate temporal lobe. Experimental Brain Research 1994;99:411–22.
[20] Gaffan D. Scene-specific memory for objects: A model of episodic memory impairment in monkeys with fornix transection. Journal of Cognitive Neuroscience 1994;6:305–20.
[21] Gaffan D. Memory, action and the corpus striatum: current developments in the memory-habit distinction. Seminars in the Neurosciences 1996;8:33–8.
[22] Gaffan D, Murray EA. Monkeys (*Macaca fascicularis*) with rhinal cortex ablations succeed in object discrimination learning despite 24-hr intertrial intervals and fail at matching to sample despite double sample presentations. Behavioral Neuroscience 1992;106:30–8.
[23] Gaffan EA, Gaffan D, Hodges JR. Amnesia following damage to the left fornix and to other sites. Brain 1991;114:1297–313.
[24] Gaffan EA, Harrison S, Gaffan D. Single and concurrent discrimination learning by monkeys after lesions of inferotemporal cortex. Quarterly Journal of Experimental Psychology 1986;38B:31–51.
[25] Gellermann LW. Chance orders of alternating stimuli in visual discrimination experiments. Journal of General Psychology 1933;42:207–8.
[26] Graf P, Squire LR, Mandler G. The information that amnesic patients do not forget. Journal of Experimental Psychology: Learning, Memory, and Cognition 1984;10:164–78.
[27] Grant DA, Berg EA. The Wisconsin Card Sorting Test. University of Wisconsin, 1948.
[28] Kessler J, Irle E, Markowitsch HJ. Korsakoff and alcoholic subjects are severely impaired in animal tasks of associative memory. Neuropsychologia 1986;24:671–80.
[29] Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit learning system in humans. Science 1996;273:1399–402.
[30] Knowlton BJ, Ramus SJ, Squire LR. Intact artificial grammar learning in amnesia. Psychological Science 1992;3:172–9.
[31] Knowlton BJ, Squire LR, Gluck MA. Probabilistic classification learning in amnesia. Learning and Memory 1994;1:106–20.
[32] Li L, Miller EK, Desimone R. The representation of stimulus familiarity in anterior inferior temporal cortex. Journal of Neurophysiology 1993;69:1918–29.
[33] Mahut H, Zola-Morgan S, Moss M. Hippocampal resections impair associative learning and recognition memory in the monkey. The Journal of Neuroscience 1982;2:1214–29.
[34] Malamut BL, Saunders RC, Mishkin M. Monkeys with combined amygdalo-hippocampal lesions succeed in object discrimination learning despite 24-h intertrial intervals. Behavioral Neuroscience 1984;98:759–69.
[35] Malkova L, Gaffan D, Murray EA. Excitotoxic lesions of the amygdala fail to produce impairment in visual learning for auditory and secondary reinforcement but interfere with reinforcer devaluation effects in rhesus monkeys. Journal of Neuroscience 1997;17:6011–20.
[36] Meunier M, Bachevalier J, Mishkin M, Murray EA. Effects on

visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. Journal of Neuroscience 1993;13:5418–32.
[37] Miller EK, Gochin PM, Gross CG. Habituation-like decrease in the responses of neurons in inferior temporal cortex of the macaque. Visual Neuroscience 1991;7:357–62.
[38] Milner B. Les troubles de la mémoire accompagnant de lésions hippocampiques bilatérales. In: Physiologie de l'Hippocampe. Paris: Centre National de la Recherche Scientifique, 1962. p. 257–72.
[39] Milner B. Some effects of frontal lobectomy in 0man. In: Warren J, Akert K, editors. The Frontal Granular Cortex and Behavior. New York: McGraw-Hill, 1964. p. 313–34.
[40] Milner B, Corkin S, Teuber HL. Further analysis of the hippocampal amnesic syndrome: 14 year follow-up study of HM. Neuropsychologia 1968;6:215–34.
[41] Mishkin M. Visual discrimination performance following partial ablations of the temporal lobe: II. Ventral surface vs. hippocampus. Journal of Comparative and Physiological Psychology 1954;47:187–93.
[42] Mishkin M, Appenzeller T. The anatomy of memory. Scientific American 1987;256:80–9.
[43] Mishkin M, Malamut B, Bachevalier J. Memories and habits: Two neural systems. In: Lynch G, McGaugh JL, Weinberger NW, editors. Neurobiology of Learning and Memory. New York: Guilford, 1984. p. 65–77.
[44] Mishkin M, Phillips RR. A corticolimbic memory path revealed through its disconnection. In: Trevarthen C, editor. Brain circuits and functions of the mind: Essays in honor of Roger W. Sperry. Cambridge: Cambridge University Press, 1990. p. 196–210.
[45] Mishkin M, Pribram KH. Visual discrimination performance following partial ablations of the temporal lobe: I. Ventral vs lateral. Journal of Comparative and Physiological Psychology 1954;47:14–20.
[46] Morris RG, Hagan JJ, Rawlins JN. Allocentric spatial learning by hippocampectomised rats: A further test of the 'spatial mapping' and 'working memory' theories of hippocampal function. Quarterly Journal of Experimental Psychology 1986;38(B):365–95.
[47] Moss M, Mahut H, Zola-Morgan S. Concurrent discrimination learning of monkeys after hippocampal, entorhinal, or fornix lesions. Journal of Neuroscience 1981;1:227–40.
[48] Murray EA, Mishkin M. Amygdalectomy impairs cross-modal association in monkeys. Science 1985;228:604–6.
[49] Orbach J, Milner B, Rasmussen T. Learning and retention in monkeys after hippocampus resection. Archives of Neurology 1960;3:230–51.
[50] Oscar-Berman M, Zola-Morgan S. Comparative neuropsychology and Korsakoff's syndrome. II: Two-choice visual discrimination learning. Neuropsychologia 1980;18:513–25.
[51] Phillips RR, Malamut BL, Bachevalier J, Mishkin M. Dissociation of the effects of inferior temporal and limbic lesions on object discrimination learning with 24-h intertrial intervals. Behavioral Brain Research 1988;27:99–107.
[52] Reed JM, Hamann SB, Stefanacci L, Squire LR. When amnesic patients perform well on recognition memory tests. Behavioral Neuroscience 1997;111:163–1170.
[53] Reed JM, Squire LR. Impaired recognition memory in patients with lesions limited to the hippocampal formation. Behavioral Neuroscience 1997;111:667–75.
[54] Rempel-Clower NL, Zola SM, Squire LR, Amaral DG. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. Journal of Neuroscience 1996;16:5233–55.
[55] Riches IP, Wilson FAW, Brown MW. The effects of visual stimulation and memory on neurons of the hippocampal formation and the neighboring parahippocampal gyrus and inferior temporal cortex of the primate. The Journal of Neuroscience 1991;11:1763–79.
[56] Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. Journal of Neurology, Neurosurgery, and Psychiatry 1957;20:11–21.
[57] Squire LR, Knowlton B, Musen G. The structure and organization of memory. Annual Review of Psychology 1993;44:453–95.
[58] Squire LR, Zola-Morgan S. The neuropsychology of memory: new links between humans and experimental animals. Annals of the New York Academy of Sciences 1985;444:137–49.
[59] Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science 1991;253:1380–6.
[60] Squire LR, Zola-Morgan S, Chen KS. Human amnesia and animal models of amnesia: Performance of amnesic patients on tests designed for the monkey. Behavioral Neuroscience 1988;102:210–21.
[61] Stern CE, Corkin S, González RG, Guimaraes AR, Baker JR, et al. The hippocampal formation participates in novel picture encoding: Evidence from functional magnetic resonance imaging. Proceedings of the National Academy of Sciences 1996;93:8660–9665.
[62] Vandeberghe R, Dupont P, Bormans G, Mortelmans L, Orban G. PET study of recognition and habit memory. Society for Neuroscience Abstracts 1995;21:275.
[63] Wang J, Aigner T, Mishkin M. Effects of neostriatal lesions on visual habit formation in rhesus monkeys. Society for Neuroscience Abstracts 1990;16:617.
[64] Wise SP. The role of the basal ganglia in procedural memory. Seminars in the Neurosciences 1996;8:39–46.
[65] Zola-Morgan S, Squire LR. Medial temporal lesions in monkeys impair memory on a variety of tasks sensitive to human amnesia. Behavioral Neuroscience 1985;99:22–34.
[66] Zola-Morgan S, Squire LR, Mishkin M. The neuroanatomy of amnesia: Amygdala-hippocampus versus temporal stem. Science 1982;218:1337–9.