

The animal model of human amnesia: Long-term memory impaired and short-term memory intact

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ABSTRACT Normal monkeys and monkeys with lesions of the hippocampal formation and adjacent cortex (the H⁺ lesion) were trained on the delayed nonmatching to sample (DNMS) task with a delay of 0.5 s between the sample and the choice. The animals with H⁺ lesions learned the task normally at this short delay and also exhibited the same pattern of response latencies as normal monkeys. This finding contrasts with previous observations that initial learning of the DNMS task with delays of 8–10 s is impaired after H⁺ lesions. The absence of an impairment at a delay of 0.5 s indicates that the H⁺ lesion does not affect short-term memory. In contrast, when monkeys with H⁺ lesions were tested at longer delays (>30 s), an impairment was observed. This selective impairment occurred when the delays were presented sequentially (from 0.5 s to 10 min) and also when delays were presented in a mixed order (1 s, 1 min, and 10 min). The data indicate that the H⁺ lesion produces a selective impairment in long-term memory, in the absence of a detectable deficit in short-term memory or perception. Accordingly, the findings confirm the long-standing idea, based primarily on studies of humans, that short-term memory is independent of medial temporal lobe function. The findings thereby establish an important parallel between memory impairment in monkeys and humans and provide additional support for the validity of the animal model of human amnesia in the monkey.

During the last decade, a model of human amnesia was developed in the nonhuman primate (1, 2). Bilateral damage to the medial temporal lobe reproduces many of the features of memory impairment in human amnesia. The structures that when damaged produce amnesia are the hippocampus and the adjacent, anatomically related perirhinal, entorhinal, and parahippocampal cortices (3). One behavioral task that has been used extensively to measure visual recognition memory in monkeys is delayed nonmatching to sample (DNMS). Performance on DNMS is sensitive to medial temporal lobe damage in both humans and monkeys (34). In this task, the animal first sees an object, and then after a prescribed delay the animal is given a choice between the previously seen (sample) object and a novel one. The animal must choose the novel object to obtain a food reward. Typically, animals are trained with a short (8–10 s) delay until they reach a criterion level of performance (90% correct for 100 trials). At this point, the delay is progressively lengthened. Monkeys with medial temporal lobe lesions exhibit an impairment that appears to become more severe as the interval between the sample and choice increases (1, 3). Poor performance when the delay between sample and choice is long suggests that the impairment is due to a loss of memory function similar to that encountered in human amnesia: the object cannot be held in memory for more than a few seconds.

Yet, it is also the case that the impairment in performing DNMS is usually accompanied by an impairment in learning the task initially—that is, animals with medial temporal lobe lesions need more trials than normal animals to learn the task, even at the short (8–10 s) delay that is typically used for training. There are at least three possible explanations for this impairment. First, the delay used for training (i.e., 8–10 s) may be too long for animals with a memory impairment to bridge effectively, with the result that more trials are needed to learn the task. It is also possible that medial temporal lobe lesions produce some cognitive impairment other than memory (e.g., a perceptual or attentional impairment) that makes the task difficult to learn. Finally, damage to the medial temporal lobe might produce both impaired long-term memory, reflected in poor performance at long delays, and impaired short-term memory, reflected in slower learning of the task.

As discussed previously, this issue is fundamental (5–8). Human amnesic patients exhibit intact short-term memory (9, 10). If medial temporal lobe lesions impair short-term memory in monkeys, then the medial temporal lesion cannot provide a valid animal model of human amnesia.

To address the issue directly, one needs to be able to test animals with very short delays between sample and choice. We developed an automated testing apparatus, based on the one described by Murray *et al.* (11), which can be used to test monkeys on DNMS with delays as short as 0.5 s. A finding of normal performance at a 0.5-s delay by monkeys with medial temporal lobe lesions would suggest that short-term memory is intact and that the 8-s delay used in the standard version of the task is too long—i.e., it is beyond the limit of short-term memory. Conversely, a finding of impaired performance at a 0.5-s delay would suggest that the lesion produces a short-term memory impairment or some cognitive impairment other than or in addition to memory.

The issue under study was earlier the subject of a commentary (7), which included a preliminary report of some of the data presented here.

METHODS

Subjects. The subjects were nine young adult cynomolgus monkeys (*Macaca fascicularis*) weighing between 4.1 and 6.8 kg at the start of this study. Based on weight-and-age tables (12, 13), these monkeys were estimated to be between 4 and 7 years of age (young adults). The nine animals consisted of two groups: four monkeys with bilateral lesions involving the hippocampus proper, the dentate gyrus, the subiculum, the posterior half of entorhinal cortex, and the parahippocampal cortex (group H⁺) and five unoperated control monkeys (group N). Fig. 1 shows a coronal section from the brain of a monkey in the H⁺ group. Prior to the present study, all animals had participated in a pilot study of visual object discrimination learning. The H⁺ animals and animals N4 and

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Abbreviation: DNMS, delayed nonmatching to sample.

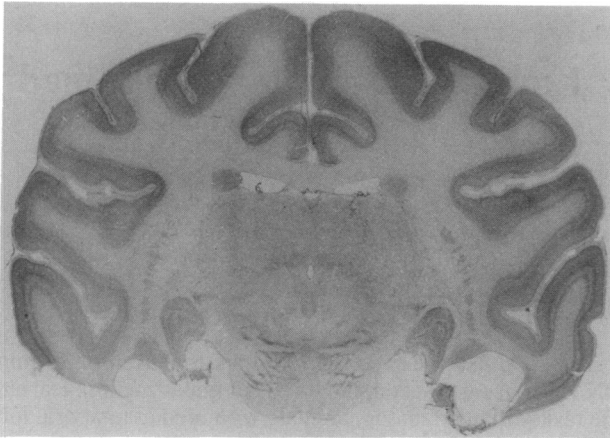


FIG. 1. Thionin-stained coronal section midway through the lateral geniculate from one monkey (H^+3) in the operated group. This animal sustained near total bilateral ablation of the hippocampal region (i.e., the cell fields of the hippocampus proper, the dentate gyrus, and the subiculum), with only slight sparing of the most anterior portion of the uncus region of the hippocampus. The parahippocampal cortex and the posterior half of entorhinal cortex were extensively damaged bilaterally. There was some sparing of the anterior entorhinal cortex bilaterally, but cells in layer II, which project to the ablated hippocampal cell fields, were completely eliminated through retrograde degeneration. The amygdaloid complex was entirely spared. Overall, this damage was similar to that described previously in monkeys with H^+ lesions prepared in our laboratory (35). In addition, perirhinal cortex sustained slight and asymmetrical damage. Inferotemporal cortex (area TE) sustained moderately severe damage on the left side and moderate damage on the right side. The posterior region of area TE on the right side was compressed by a moderate enlargement of the lateral ventricle. There was also slight and asymmetrical damage to the anterior ventral portion of visual cortex. Histological examination of the brain from a second monkey (H^+4) indicated that damage was similar to what was observed in monkey H^+3 , except that damage to area TE and the visual cortex was minimal. Monkey H^+4 required more trials than any of the other monkeys to reach performance criterion during training on the basic task. This monkey experienced motivational problems throughout testing and was not tested on mixed delays. Analysis of magnetic resonance images from the two other operated monkeys indicated bilateral and extensive damage to the hippocampal region and adjacent entorhinal and parahippocampal cortex. ($\times 1.57$.)

N5 had also participated in a formal study of memory for simple object discriminations (4). In addition, animals N1–N3 had been tested on a battery of five tasks, including the standard, manually administered version of DNMS (animals N4–N6 in ref. 14). None of the animals had had any experience with the automated test apparatus described below.

Test Apparatus. An 80286-IBM compatible computer operated a touch-sensitive monitor screen (Microtouch Systems, Woburn, MA) and an automatic pellet dispenser (11). Individual stimuli displayed on the monitor were composed of two superimposed ASCII characters of different shape, size, and color. A contact by the monkey within a 5×6 cm rectangular area centered on the stimulus counted as a response. Correct responses were followed by the delivery of a reward (190-mg banana-flavored monkey pellet; P. J. Noyes, Lancaster, NH) into a small hopper located 5 cm directly below the center of the monitor.

DNMS. Monkeys were initially pretrained in four stages to use the apparatus. They were first trained to retrieve rewards from the hopper, then to touch a stimulus when it was presented in the center of the monitor screen, then to touch the stimulus within 60 s to obtain a reward, and finally to touch a stimulus on the left, center, or right of the screen within 30 s.

Initial Learning. A sample stimulus was presented in the center of the screen for 20 s (sample phase). If the monkey touched the stimulus, the screen became blank for 0.5 s and then the choice phase began. The sample stimulus was not rewarded. If the monkey did not touch the sample, the screen blanked, and the next intertrial interval (20 s) began. For the choice phase, the sample stimulus and a novel stimulus appeared on the left and right sides of the screen at a distance of 8.2 cm from the center. Whether the sample appeared on the left or right side varied according to a predetermined, pseudorandom schedule (16). If the monkey responded correctly—i.e., it touched the novel stimulus within 20 s—the screen blanked, two banana pellets were delivered, and the intertrial interval began. If the monkey did not respond within 20 s or responded incorrectly—i.e., it touched the sample stimulus—the screen blanked, no reward was delivered, and the intertrial interval began. Monkeys were trained until they reached a learning criterion of 90% correct performance or better within five consecutive sessions (200 trials). The animal's responses and response latencies were recorded by the computer.

Sequential Delay Testing. After the learning criterion had been reached, the delay interval was increased consecutively to 4 s, then to 8 s, 15 s, 60 s, 3 min, and 10 min. Two hundred trials (40 trials a day for 5 days) were given at each of the 4-, 8-, and 15-s delays. One hundred trials were given at the 60-s delay (20 trials a day for 5 days) and the 3-min delay (10 trials per day for 10 days). Fifty trials were given at the 10-min delay (5 trials per day for 10 days).

Mixed Delay Testing. Monkeys were next tested using delays of 1 s, 1 min, and 10 min presented in a mixed order. Specifically each delay was presented for a block of 3 days before moving to the next delay, and the order in which the delays were presented was balanced within and between monkeys. For the 1-s and 1-min delays, 60 trials per block were given (20 trials per day); for the 10-min delay, 15 trials per block were given (5 trials per day). Monkeys received a total of two blocks at the 1-s and 1-min delays and a total of four blocks at the 10-min delay. Only four normal and three H^+ monkeys were given mixed delay testing.

RESULTS

Animals with H^+ lesions learned at the same rate as N animals to work with the apparatus and to obtain rewards during the four stages of pretraining. A two-way ANOVA (group by stage, as measured by the number of daily training sessions required to complete each stage) revealed no significant effects ($F < 1.0$, $P > 0.10$).

Initial Learning. Table 1 and Fig. 2 show the number of trials needed by the monkeys in group N and group H^+ to reach 90% correct performance with the 0.5-s delay. The groups performed similarly, as measured by trials to criterion [$N = 2011$, $H^+ = 2837$; $t(7) = 0.64$, $P > 0.50$] and errors to criterion [$N = 721$, $H^+ = 943$; $t(7) = 0.46$, $P > 0.50$]. Fig. 3 shows the mean latencies for responses during the sample and choice phases, averaged across all training trials. A two-way ANOVA (group \times response type) indicated that responses on the choice trial ($N = 1.2$ s, $H^+ = 1.0$ s) were faster than responses to the sample [$N = 2.8$ s, $H^+ = 2.3$ s; $F(1, 7) = 47.2$, $P < 0.001$]. There was no effect of group [$F(1, 7) = 2.31$, $P > 0.10$], and no interaction between group and response type [$F(1, 7) = 1.1$, $P > 0.10$]. Additional analyses indicated that the latency to respond at the start of training (first 100 trials; $N = 3.6$ s, $H^+ = 2.3$ s) was greater than when criterion performance was reached (last 100 trials; $N = 1.2$ s, $H^+ = 1.3$ s; $P < 0.05$). There were no differences between the groups and no interaction between group and stage of training ($P > 0.10$). In summary, as measured by trials and errors to criterion as well as by response latencies, the H^+ group was

Table 1. Learning and performance scores

	Initial learning		Sequential delay testing					Mixed delay testing			
	Animal	Trials	Errors	0.5 s	4 s	8–15 s	30 s–1 min	3–10 min	1 s	1 min	10 min
N1		701	244	92	87	85	82	77	95	86	75
N2		3700	1509	92	84	79	78	67	—	—	—
N3		1631	419	93	97	89	79	68	96	89	60
N4		2625	959	90	80	70	66	67	98	88	62
N5		1398	476	93	77	80	81	67	94	87	67
Mean N		2011	721	92	85	81	77	69	96	88	66
H ⁺ 1		517	144	93	91	83	68	69	98	86	60
H ⁺ 2		1539	567	90	78	75	71	62	98	79	59
H ⁺ 3		2830	804	90	68	75	65	59	94	82	55
H ⁺ 4		6460	2258	91	79	70	70	53	—	—	—
Mean H ⁺		2837	943	91	79	76	69	61	97	82	58

Scores are given for the monkeys in the N and H⁺ groups on the DNMS task for initial learning, for the performance test when delays were presented sequentially (Sequential delay testing), and for the performance test when delays were presented in a mixed order (Mixed delay testing). The Trials and Errors scores are the number of trials and errors required to reach learning criterion during initial learning. The scores for delays are the percent correct scores for the indicated delays. Animals N5 and H⁺4 were not tested on the mixed delay paradigm.

indistinguishable from the N group in learning the DNMS task at the 0.5-s delay.

Sequential Delay Testing. Table 1 shows the performance of the H⁺ and N groups as the delay intervals were increased sequentially from 0.5 s to 10 min. The data for the 0.5-s delay were not included in the analyses because these data simply represent the final trials of training. Except for the 4-s data, the data from adjacent delay intervals were averaged as indicated in Table 1. An ANOVA involving two groups and four delays (4 s, 8–15 s, 30 s–1 min, and 3–10 min) revealed a significant effect of group [$F(1, 7) = 5.49, P = 0.05$] and delay [$F(2, 14) = 23.59, P < 0.001$] and no significant group \times delay interaction [$F(2, 14) = 0.62, P > 0.50$]. Separate comparisons between the N group and the operated group at each of the delay intervals revealed that the H⁺ group was unimpaired at the short-delay intervals [4 s: N = 85% correct, H⁺ = 79% correct, $t(7) = 1.0, P > 0.30$; 8–15 s: N = 81% correct, H⁺ = 76% correct; $t(7) = 1.2, P > 0.20$] and impaired at the longer-delay intervals [30 s–1 min: N = 77% correct, H⁺ = 69% correct, $t(7) = 2.7, P < 0.05$; 3–10 min: N = 69% correct, H⁺ = 61% correct, $t(7) = 2.2, P = 0.05$].

Response latencies during sequential delay testing (Fig. 4) were analyzed with a three-factor ANOVA (group \times response type \times four delays). There was an effect of response

type (sample vs. choice) [$F(1, 7) = 47.9, P < 0.001$] and delay [$F(1, 7) = 66.0, P < 0.001$] but no effect of group ($F < 1.0$) and no interaction involving the group factor ($F < 1.0$). The significant response type \times delay interaction [$F(3, 21) = 9.6, P < 0.001$] indicated that as the delay increased the response latency for the sample phase increased more than the response latency for the choice phase.

Mixed Delay Testing. Fig. 5 shows the performance of the N and H⁺ groups when the delays were presented in the mixed block design. As in the case when delays were presented sequentially, an analysis of variance (two groups and three delays) revealed an effect of group [$F(1, 5) = 8.42, P < 0.05$] and delay [$F(2, 10) = 142.52, P < 0.001$] and no group \times delay interaction [$F(2, 10) = 2.43, P > 0.10$]. Separate comparisons between the normal group and the H⁺ group at each of the three delay intervals indicated that the H⁺ group was unimpaired at the 1-s delay [N = 96% correct, H⁺ = 97% correct; $t(5) = 0.61, P > 0.50$] and impaired at the 1-min delay [N = 88% correct, H⁺ = 82% correct; $t(5) = 2.8, P < 0.05$]. At the 10-min delay, the performance of the H⁺ group was numerically worse than that of the normal group, but this difference did not reach significance [N = 66% correct, H⁺ = 58% correct, $t(5) = 1.9, P = 0.11$], presumably due to the unusually large variance in the N group.

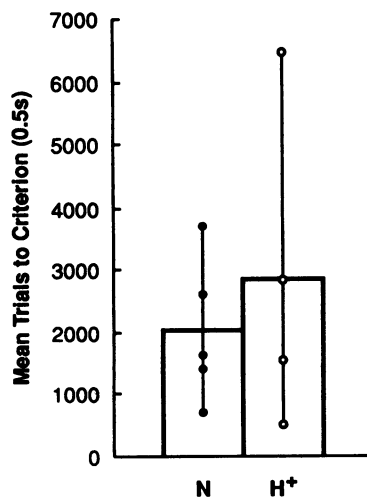


FIG. 2. Initial learning of the DNMS task with a delay of 0.5 s for normal monkeys (N) and monkeys with bilateral lesions of the hippocampal region, the posterior entorhinal cortex, and the parahippocampal cortex (H⁺). Symbols show scores for individual animals.

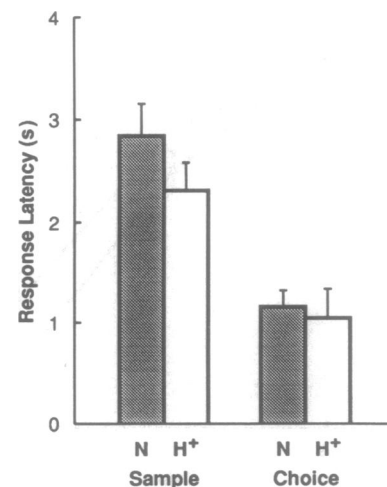


FIG. 3. Mean response latencies to the sample and choice trials during initial learning of the DNMS task for normal monkeys (N, shaded bars) and monkeys with H⁺ lesions (open bars). Error bars show the standard error of the mean.

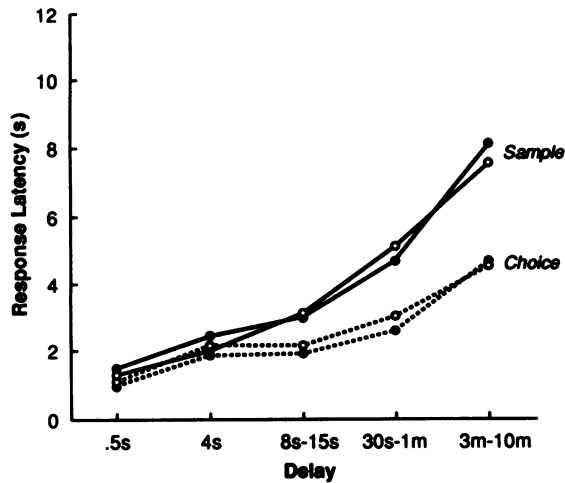


FIG. 4. Mean response latencies to the sample phase (solid lines) and choice phase (dashed lines) during performance of the DNMS task by normal monkeys (N, ●) and monkeys with H⁺ lesions (○). The delays were increased sequentially from 0.5 s to 10 min.

To compare directly the findings from the short (1-s) delay and the two long (1 min and 10 min) delays, an ANOVA was also carried out involving two groups and two delays (1 s and the average of the 1-min and 10-min delays). This revealed a significant effect of delay [$F(1, 5) = 316.9, P < 0.001$] and a significant group \times delay interaction [$F(1, 5) = 8.61, P < 0.05$]. The effect of group approached significance [$F(1, 5) = 5.33, P = 0.07$]. The H⁺ group was significantly impaired at the long delays [70% correct vs. 77% correct; $t(5) = 3.3, P < 0.05$].

Finally, the mixed delay data were also evaluated with signal detection analyses, using an unbiased measure of discriminability (d') (17). For the application of d' scores to data from the DNMS test, see Ringo (5). An analysis of variance based on d' scores (two groups \times three delays) yielded a significant effect of delay [$F(2, 10) = 148.3, P < 0.001$] and a group \times delay interaction that fell just short of significance [$F(2, 10) = 3.65, P < 0.07$]. The results were similar when the data from the two long delays were averaged and the ANOVA was repeated. There was an effect of delay [$F(1, 5) = 192, P < 0.001$] and a marginal group \times delay interaction [$F(1, 5) = 6.05, P < 0.06$].

The response latencies during mixed delay testing were similar for the two groups ($P > 0.10$).

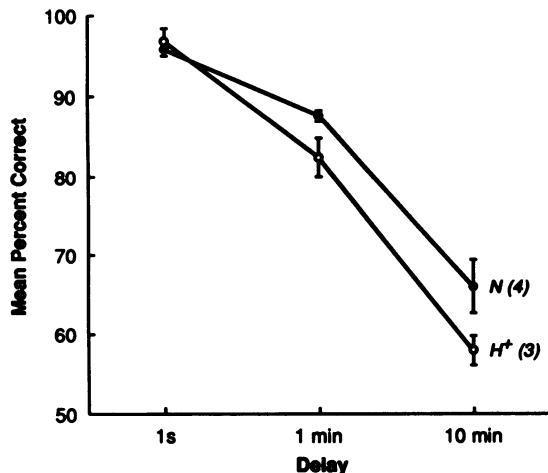


FIG. 5. Mean percent correct performance for normal monkeys (N, ●) and H⁺ monkeys (○) on the DNMS task when the delay intervals were presented in a mixed order. Error bars show the standard error of the mean.

DISCUSSION

Monkeys with bilateral lesions of the hippocampal formation (the H⁺ lesion) learned the DNMS task as well as normal monkeys when the delay between sample and choice was very short (0.5 s). In addition, during the sample and choice phases of the training trials, H⁺ monkeys exhibited the same pattern of response latencies as normal monkeys.

In contrast to their intact performance at the 0.5-s delay, the H⁺ monkeys were impaired when the delay between sample and choice was lengthened to 30 s or more. The impairment was observed at long delays both when the delay trials were presented sequentially and when the delays were presented in a mixed order. The normal monkeys exhibited forgetting as the delay was increased, but the H⁺ monkeys exhibited more forgetting than the normal monkeys. The mixed delay condition was important because of the possibility that, when delays are presented sequentially, a deficit at the long delays might be due to some factor other than the length of the delay. For example, as the delays were increased and animals gained more experience with the task, normal animals might have acquired strategies that enhanced their performance while H⁺ animals could not. The mixed delay condition avoids this problem. Finally, the response latencies were virtually identical for H⁺ and normal monkeys during the sample and choice phases of the test trials.

Thus, an impairment appeared selectively at long retention intervals but not at very short retention intervals. The impairment cannot be attributed to some perceptual or cognitive deficit, because such a deficit should have impaired performance at short delays as well as at long delays. Rather, the H⁺ lesion appears to reproduce in monkeys a key feature of human amnesia—namely, intact short-term memory and impaired long-term memory. This same conclusion was reached in an earlier study in which monkeys with large medial temporal lobe lesions performed normally on DNMS when training was given preoperatively and postoperative testing was carried out at very short delays (8).

The idea that short-term memory and long-term memory can be dissociated in experimental animals, whether by lesions or by other methods, has been questioned recently (5, 6). This is surprising, as elegant demonstrations of this distinction can be found in earlier work with rodents, pigeons, and monkeys (18–21). Moreover, the distinction between short-term and long-term memory has been well established in the literature of human neuropsychology during the past four decades (9, 10, 22, 23). In humans, bilateral damage to medial temporal lobe or diencephalic structures produces global amnesia, which spares short-term memory but impairs the ability to establish a usable long-term memory.

It is worth considering further why the idea that medial temporal lobe lesions selectively impair long-term memory might seem peculiar. As Horel (ref. 6, p. 9) wrote, "... long-term memory is part of the cortical areas where the information to be remembered is processed and perceived." If one takes this view, which is widely accepted (1, 23, 24), then it might seem inconsistent to propose that the medial temporal lobe is involved in long-term memory but not in processing or perceiving. Stated differently, neocortical lesions cause domain-specific information-processing deficits (e.g., prosopagnosia, aphasia) and corresponding domain-specific memory deficits (e.g., for faces or words). Moreover, lesions of specific neocortical areas should always impair performance at very short delays as well as at long delays, within the domain of information processing for which that area of neocortex is specialized. In contrast, medial temporal lobe lesions appear to cause global memory impairment without any corresponding impairment in information pro-

cessing, and medial temporal lobe lesions impair performance at long delays but not at very short delays.

The cognitive effects of medial temporal lobe lesions can be understood in terms of the kind of computation that this brain region appears to carry out. Perception and short-term memory are thought to depend on coordinated activity within the neocortex. It has been suggested that, at the time of learning, the medial temporal lobe system establishes functional connections with widely distributed areas of neocortex, based on synaptic changes within this system that occur as a part of learning (23). Medial temporal lobe structures need to operate in concert with neocortex, if short-term activity in neocortex is to be transformed into long-term, permanent memory (25–28, 36). By this scenario, medial temporal lobe damage spares short-term memory because short-term memory can be supported by the neocortex, and an impairment is produced that appears selective to long-term memory. The function of the medial temporal lobe is to provide for an evolutionarily late cognitive ability—the ability to store, retrieve, and operate on declarative knowledge (23, 29). Because of how the computation is organized in the brain, anatomically and functionally, damage to the medial temporal lobe produces a syndrome that can be appropriately described in terms of memory problems.

If the medial temporal lobe can be understood as having memory functions, it should be possible to distinguish its contribution from that of other cortical areas. As Horel wrote (ref. 6, p. 5), there should be “measures that differentiate [its function] from other functions.” Indeed, a review of the behavioral effects of medial temporal lobe damage identifies three defining features of medial temporal lobe function. First, as shown in the current study and in an earlier one (8), the lesion dissociates short-term and long-term recollection. This distinction arises naturally from the kind of computation that the medial temporal lobe is involved in.

A second defining feature of medial temporal lobe function is that it is involved in memory for a limited period of time after learning. Gradually over time memory is reorganized (or consolidated), and storage in neocortex eventually becomes independent of the medial temporal lobe system. As a result, a lesion within this system that is sufficiently delayed after learning does not produce retrograde amnesia. Four prospective studies in monkey, rat, and mouse have demonstrated this effect—i.e., temporally graded retrograde amnesia (4, 30–32). In contrast, there is no evidence for temporally graded retrograde amnesia following a lesion in neocortex.

A third defining feature of medial temporal lobe function is that damage produces memory impairment that is multimodal—i.e., memory is globally impaired regardless of the sensory modality in which information is presented (15, 33). In contrast, the memory problems associated with neocortical lesions are domain-specific—i.e., they are specific to the kind of material that is ordinarily processed by the damaged area.

In summary, the present study confirms a key feature of medial temporal lobe function in the nonhuman primate. It is essential for long-term memory but not for short-term memory. Following damage to the medial temporal lobe in the monkey, short-term memory is intact, just as it is after similar damage in humans.

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