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# Selective Hippocampal Damage in Rhesus Monkeys Impairs Spatial Memory in an Open-Field Test

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**ABSTRACT: The hippocampus is critical for remembering locations in a wide variety of species, including humans. However, recent findings from monkeys following selective hippocampal lesions have been equivocal. To approximate more closely the situations in which rodents and birds are tested, we used a spatial memory task in which rhesus monkeys (*Macaca mulatta*) moved about freely in a large room, on a tether. We used MRI-guided stereotaxic surgery to produce selective hippocampal lesions in five monkeys, and retained five unoperated control monkeys. In the study phase of each trial of the matching-to-location task, monkeys found food in one site in an array of identical foraging sites. During the test, which occurred after a delay, monkeys could return to the site where the food had been found during study to obtain more food. In Experiment 1, normal monkeys showed a small significant tendency to return directly to a site where they had previously found food that day. Operated monkeys showed no such matching tendency. In Experiment 2, further training produced reliable matching-to-location performance in both groups at short delays, but monkeys with selective hippocampal lesions rapidly forgot the location of the food. In Experiment 3, we tested whether monkeys used a "cognitive map" to encode the location of the hidden food, by requiring them to relocate the food from a starting location different from that used during study. As a group, monkeys were more accurate than expected by chance, indicating that they did encode the rewarded location with respect to allocentric landmarks; however, both groups of monkeys were significantly worse at relocating the food when required to approach from a different location. In Experiment 4, probe trials using symmetrical test arrays found no evidence for egocentric coding of the rewarded location.** © **2004 Wiley-Liss, Inc.**†

**KEY WORDS: navigation; macaque; primate; temporal lobe; retention**

## INTRODUCTION

The hippocampus plays a critical role in spatial memory in distantly related vertebrate species, indicating that spatial information processing is an ancient hippocampal phenotype that has been conserved over hundreds of millions of years of evolution (Rodríguez et al., 2002a). Representative species from the four vertebrate classes that have been studied—birds, reptiles, bony fish, and mammals—show hippocampal dependent spatial memory function. Specifically, damage to the hippocampus, or the presumed homologue of the hippocampus, causes deficits in spatial memory in songbirds and pigeons (Sherry and Vaccarino, 1989; Hampton and Shettleworth, 1996a,b; White et al., 2002; for review, see Sherry and Duff, 1996; Colombo and Broadbent, 2000), lizards and turtles (Day et al., 2001; Rodríguez et al., 2002b), goldfish (Lopez et al., 2000; Rodríguez et al., 2002b), and rats (e.g., Nadel, 1991; Redish, 2001). Furthermore, humans with relatively selective hippocampal lesions are also impaired on at least some spatial memory tests (Bohbot et al., 1998; Kessels et al., 2001), and the human hippocampus is activated by both virtual (Maguire et al., 1998; Grön et al., 2000) and imagined (Maguire et al., 1997) spatial navigation. However, findings concerning the functional effects of selective ablation of the hippocampus (lesions that spare the underlying parahippocampal cortex) on spatial memory in monkeys have been equivocal, with most studies finding no impairment (Ridley et al., 1997; Murray and Mishkin, 1998, Experiment 2; Murray et al., 1998, Experiment 1; Málková and Mishkin, 2003), but others reporting a deficit (Murray et al., 1998, Experiment 2; Beason-Held et al., 1999, delayed recognition span task, spatial condition).

One possible reason for the preponderance of negative findings in nonhuman primates is that the tests used with monkeys differ dramatically in relative spatial scale from those used with rodents and birds. In contrast with the tests with smaller animals, monkeys were not required to navigate through space in a testing arena many times their own body size, but rather responded by reaching out to the test stimuli from a single body position. An earlier study motivated by this logic found that fornix transection, which interrupts afferents and efferents of the hippocampal formation, impaired spatial delayed nonmatching-to-sample in a large T-maze in which monkeys moved bodily from place to place (Murray et al., 1989). To evaluate further the idea that locomotion facilitates engagement of the hippocampus in spatial tasks, and to assess the effects of selective hippocampal lesions on spatial memory, we developed a task in which monkeys were free to move around in a large room, thus more closely approximating both the experimental conditions used with smaller animals and, presumably, the conditions that macaques routinely encounter in nature.

## MATERIALS AND METHODS

### Subjects

Ten experimentally naïve rhesus monkeys (*Macaca mulatta*), 8 males and 2 females, were used. Monkeys ranged from 3.1 to 5 years of age (mean = 3.6) and from

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4.6 to 7.6 kg (mean = 5.6) at the beginning of the experiment. Monkeys were housed in single-sex, socially compatible pairs, with one monkey in each pair randomly assigned to the surgery condition and the other monkey to the control condition. Preferred foods were used as rewards to minimize the need for diet restriction. Before testing each day a screen divider was placed in the home cage to separate each pair. After testing, monkeys were fed while still separated to prevent food competition, and then repaired after all food had been consumed. Water was continuously available in the home cage.

## Surgery

Five monkeys received bilateral excitotoxic lesions of the hippocampus. Stereotaxic coordinates for the injection of excitotoxin were generated using magnetic resonance imaging (MRI) as described elsewhere (Saunders et al., 1990; Alvarez-Royo et al., 1991; Murray and Mishkin, 1998; Hampton et al., 2004). Up to 2 weeks prior to surgery, each animal was anesthetized with a combination of ketamine hydrochloride (8.5 mg/kg) and xylazine (0.35 mg/kg) and was positioned in an MRI-compatible stereotaxic frame. A T1-weighted scan was obtained from each monkey (SPGR, TE6, TR25, flip angle 30, NEX 4, 256 square matrix, FOV 100 mm, 1-mm slices) and the resultant images used to determine stereotaxic coordinates for the hippocampal injections. To ensure that the head could be repositioned in the stereotaxic frame for surgery just as during the scans, a specially designed pointer mounted on a micromanipulator was used to determine the stereotaxic coordinates of landmarks on each of the monkeys' lateral incisors.

At the time of surgery, monkeys were sedated with either ketamine hydrochloride (10 mg/kg; monkeys Ch, Sd, Md, Sm) or a combination of valium (0.6 mg/kg) and medetomidine hydrochloride (0.23 mg/kg; Domitor, Pfizer; a xylazine-like $\alpha 2$ adrenergic agonist; monkey Qq). Atropine (0.1 mg/kg) was administered to prevent bradycardia and excessive salivation during intubation. Anesthesia was maintained with isoflurane (1.0–3.0%, to effect). After the one monkey receiving medetomidine hydrochloride had been placed on isoflurane gas anesthesia, the medetomidine was reversed with atipamezole (0.5 mg/kg; Antisedan, Pfizer). Aseptic procedures were employed, and heart rate, respiration rate, blood pressure, expired $CO_2$, and body temperature were monitored throughout the procedure. In addition, the monkeys received an intravenous drip of isotonic fluids throughout surgery.

A midline incision was made, a large bone flap was turned, and small slits made in the dura to permit penetration of the injection needle. Ibotenic acid (0.09 M; ~20 μl per hemisphere) was injected bilaterally into the hippocampus and subiculum of four of the five experimental monkeys (Ch, Sd, Md, Sm) using a dorsal approach, as described previously (e.g., Murray and Mishkin, 1998), with the exception that bilateral injections were made simultaneously in a single stage, rather than in two separate stages. In the fifth monkey (Qq), we used a different method. A small opening was made in the cranium slightly dorsal to the nuchal line, and N-methyl-D-aspartate (NMDA) (0.4 M; ~20 μl per hemisphere) was injected into the hippocampus along a single needle track via an occipital approach (Hampton et al., 2004). After the injections were completed, the opening was closed in anatomical layers. In this monkey, the surgery was carried out in two stages separated by 6 weeks.

Dexamethasone sodium phosphate (0.5 mg/kg) and cefazolin were administered one day before surgery and for 1 week after surgery to reduce inflammation and to prevent infection, respectively. At the end of surgery, and for 2 additional days, the monkeys received the analgesic ketoprofen (10–15 mg bid); acetaminophen (10 mg/kg, bid) was provided for 5 additional days.

Within 2 weeks after surgery, monkeys were given T2-weighted scans (2-D spin echo pulse sequence, TE 17, TE2 102, TR 3000, NEX = 3, FOV 11 cm, 1.5-mm slices) to assess the efficacy of the injections. Follow-up surgeries were undertaken to complete lesions where the injections were determined to have been ineffective (Málková et al., 2001).

## Lesion Assessment

The extent of shrinkage visible in MRI correlates with damage estimates generated by traditional histological methods (Málková et al., 2001; Nemanic et al., 2002). Málková et al. (2001) quantified the relationship between MRI-derived hippocampal volume estimates and hippocampal damage in a large group of monkeys that had received excitotoxic lesions of the hippocampus, thus making it possible to estimate the extent of hippocampal damage from in vivo MRI. Because our monkeys are still engaged in behavioral testing, we used the technique described by Málková et al. (2001) to estimate the extent of the hippocampal damage in these animals. Accordingly, we obtained final postoperative scans for each monkey 62 to 536 days after the last surgery (mean = 294.6 days), when hippocampal shrinkage is virtually complete (Málková et al., 2001). The surface area of each 1-mm section of the hippocampus in the preoperative MRI of each monkey was determined using Scion Image (Scion, Frederick, MD). Each hippocampus was measured on three separate occasions, and the average of the three was used as the final value. The same procedure was applied to postoperative scans. From these two measurements, the reduction in hippocampal volume was determined. Finally, to estimate the overall percent damage, this value was then entered into the regression function generated by Málková et al. (2001):

$$\text{Percentage cell loss} = (\text{percentage volume loss}/0.757) - 3.2$$

As shown in Table 1, the estimated damage to the hippocampus in our five operated monkeys ranged from 65–85%. Figure 1 shows representative preoperative, T2-weighted, and final postoperative MR images for one monkey in the operated group (Sd).

## Testing Room

Testing was conducted in a large room (4.0 × 5.1 m). One corner of the room was occupied by the experimenter and was separated from the rest of the room by a chain-link fence (Fig. 2). The fence was covered with tarpaulin so that the monkeys could not see the experimenter. A camera was mounted high on the wall of the testing area, permitting observation of the monkeys via closed-circuit television. For each session, a monkey was brought to the testing room in a large wheeled transport cage, which was

*TABLE 1.*

*Estimated Extent of Hippocampal Damage in Five Operated Monkeys*

| Monkey[a] | Additional surgeries[b] | Sx to final scan[c] (days) | % volume lost[d] | | | Estimated cell loss[e] (%) |
|---|---|---|---|---|---|---|
| | | | Left | Right | Mean | |
| Md | 2 | 97 | 62.3 | 47.1 | 54.7 | 69.1 |
| Sd | 1 | 62 | 70.1 | 55.6 | 62.8 | 79.8 |
| Sm | 1 | 528 | 73.4 | 59.7 | 66.5 | 84.7 |
| Qq | 0 | 250 | 61.9 | 70.6 | 66.3 | 84.3 |
| Ch | 2 | 536 | 65.5 | 38.1 | 51.8 | 65.3 |
| Mean | 1.2 | 295 | 66.6 | 54.2 | 60.4 | 76.6 |

[a]Subjects receiving excitotoxic lesions of the hippocampus.
[b]Number of follow-up surgeries performed based on MRI assessment that the lesion was not adequate.
[c]Number of days between the last surgery and the final MRI scan.
[d]1 − (postoperative hippocampal/preoperative volume) determined from MRI.
[e]Calculated according to Málková et al. (2001).

secured to the wall in one corner of the room. A tether that connected via a system of pulleys to the opposite corner of the room was clipped onto the monkey's collar. This arrangement permitted the experimenter to pull the monkey in the direction of the transport cage if necessary. The monkeys moved about freely on the tether, and retrieved food from "foraging sites," each consisting of a 25-lb weight-lifting plate covered with an inverted plastic flowerpot that could easily be displaced to reveal the food hidden underneath (Fig. 3).

## EXPERIMENT 1

We measured the tendency of monkeys to match to location spontaneously, without explicit training. On the first trial, the only indication monkeys were given that they should employ a matching rule was that they discovered a large amount of food in one of the foraging sites and were not permitted to finish it before returning to the transport cage. On subsequent trials, monkeys also had the opportunity to learn from trial and error that a matching rule was in effect.

### Pretraining

Prior to the main task, monkeys were adapted to retrieving a mixture of nuts and dried fruit scattered on the floor. Once they would readily exit the transport cage and collect food from the floor, they were trained to displace the inverted flowerpot and retrieve food from a single foraging site placed in trial-unique locations in the room. Because the location of the single baited site changed on every run, monkeys did not return to a particular site, and so were not given the opportunity to learn a matching to location rule. Once monkeys reliably approached the foraging site and collected food in under 10 min, they moved on to the next stage.

### Main Task

Each trial consisted of a study phase, during which monkeys could learn the location of the food on that trial, followed by two test phases, one 5 min and the other 4 h later.

#### *Study phase*

A single array of four identical foraging sites, in which the sites were equidistant from the position of the monkey transport cage, was used throughout Experiment 1. For each trial, a single site was randomly assigned to contain the food reward. For randomization, a pool in which each of the four locations was represented twice was drawn from without replacement. Before the monkey was brought to the room, the chosen site was baited with a large portion of the nut and dried fruit mix, and all sites were covered with the inverted flowerpots. Monkeys were released from the transport cage and allowed to search freely in the four foraging sites until they located the hidden food. The order and number of "looks" made by the monkeys were recorded. A look was defined as lifting a flowerpot, whether or not the flowerpot was actually removed. After looking in the target site, monkeys were allowed to take five pieces, or one handful, of the food and were then returned to the transport cage. Thus, the monkeys could know that a large portion of food remained at the baited site. A tarpaulin was then positioned to block the monkey's view of the foraging sites.

#### *Test phase*

A false baiting procedure was used, in which a flowerpot was removed and replaced on every site, in the same order every trial, to prevent auditory cues from directing the monkey to the correct (baited) site. After a delay of 5 min, the tarpaulin was removed from the cage and the monkey was allowed to search for the food until finding it. The order and number of looks made in finding the target site were again recorded. A correct response was defined as looking first under the flowerpot that contained food during the

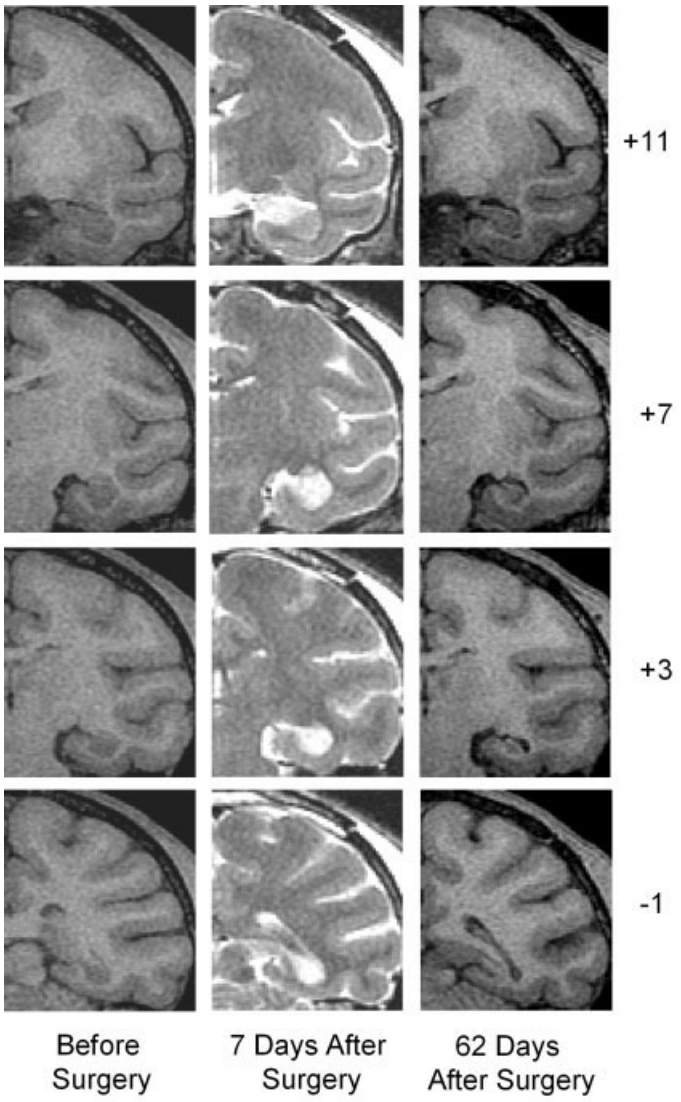


**FIGURE 1. MRI images of monkey Sd. The left, middle, and right columns show the right hemisphere before surgery (T1-weighted scan), 7 days after surgery (T2-weighted scan), and 62 days after the last surgery (T1-weighted scan). In the T2-weighted scan taken postoperatively edema resulting from the neurotoxin injections appears as "hypersignal," the white area in the region of the hippocampus. Numerals on the right indicate approximate distance in millimeters from earbar 0.**

study phase of that trial. After it had eaten another portion of the food, the monkey was returned to the transport cage and then to the home cage; 4 h later, the test procedure was repeated. Each monkey participated in 25 trials, administered at a rate of 1 trial per day, 5–6 days per week.

## Results

The tendency of monkeys to match to location was assessed as the proportion of correct first looks. These scores were arcsine-transformed to achieve better conformation to the assumptions of analysis of variance (ANOVA). During the study phase of each trial, when monkeys had to guess the location of the food, both

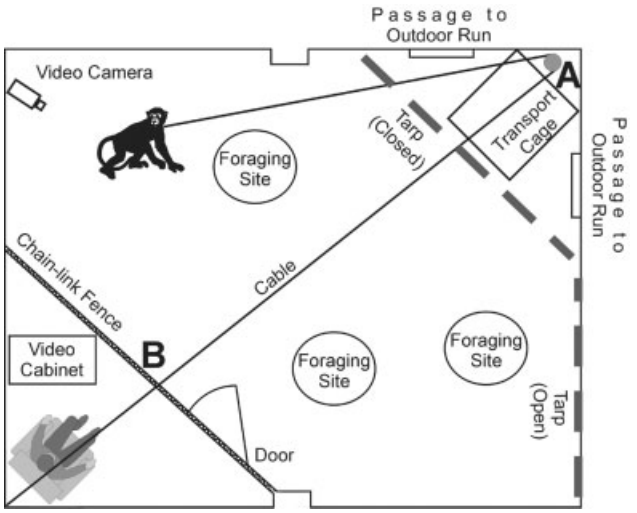


**FIGURE 2. Schematic diagram of the test room (4.0 × 5.1 m), indicating the location of the observer, the tether system by which monkeys could be returned to their transport cage, and a representative array of foraging sites. A tarp prevented monkeys from seeing the experimenter and a closed-circuit video system was used to observe the monkeys. Objects are not to scale. A,B: Positions of the transport cage used in Experiments 3 and 4.**

groups performed near chance (25%) (Fig. 4). In the retention tests, intact monkeys performed slightly better than chance, demonstrating some memory for the location of the food. By contrast, monkeys with excitotoxic lesions of the hippocampus failed to show any improvement over chance. A repeated measures ANOVA confirmed that control monkeys retained more information about the location of the food found during the study phase of trials than did operated monkeys (trial phase × Group: $F_{2,16} = 5.37$, $P < 0.05$; trial phase: $F_{2,16} = 13.05$, $P < 0.01$; Group: $F_{1,8} = 1.14$). Separate analysis of the two groups confirmed that whereas control monkeys found the food on the first look significantly more often at test than at study ($F_{2,8} = 10.95$, $P < 0.01$) monkeys with hippocampal lesions did not ($F_{2,8} = 2.18$).

**FIGURE 3. Photographs of a monkey approaching a foraging site (left) and displacing the inverted flowerpot to procure food hidden underneath (right).**

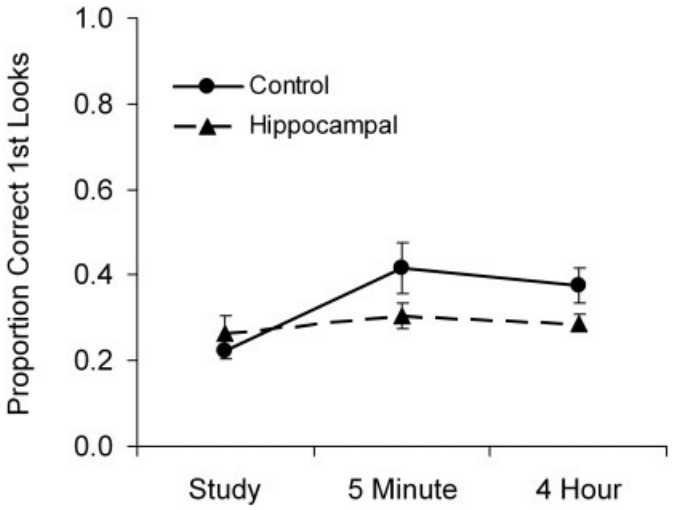


**FIGURE 4. Spontaneous spatial matching-to-sample. Proportion of first looks made to the (baited) target foraging site by intact (circles, solid line) and operated (triangles, dashed line) monkeys in Experiment 1. During study, the monkeys did not know where the food was located, and therefore all monkeys performed near the chance level of 25%. The tendency to match to location is indexed by the degree to which the monkeys were more likely to find the food on the first look when returned to the testing room after 5 min and 4 h. Control, unoperated monkeys (N = 5); hippocampal, monkeys with selective hippocampal lesions (N = 5).**

## EXPERIMENT 2

In Experiment 1, although the control group performed above chance, the spatial foraging task did not yield robust spontaneous matching-to-location behavior. In Experiment 2, therefore, we examined whether explicit training with the matching rule, under simplified conditions, would increase accuracy. Several changes were made in an effort to facilitate accurate performance. First, the monkeys were trained with much shorter delays than those used in Experiment 1. Second, rather than using the fixed array of four sites each day, we used trial-unique configurations of three foraging sites to prevent interference between consecutive trials (Wright et al., 1986). Third, we no longer required the monkeys to search by trial and error for the food during the study phase, but rather had the reward clearly visible at the target site. Finally, monkeys received more than one trial each day, allowing us to provide each monkey with more opportunity to learn. After monkeys acquired the matching rule under these new conditions, we compared the performance of control and operated monkeys using a delay titration procedure in which the interval between the study and test phases of each trial was gradually increased.

### Materials and Methods

#### *Subjects*

These were the same monkeys that took part in Experiment 1. The monkeys had some additional experimental experience between the end of Experiment 1 and the beginning of Experiment 2, the results of which are not reported here.

#### *Testing room*

This is the same testing room used in Experiment 1.

#### *Acquisition*

There were four stages of acquisition. Stage 1 taught monkeys the matching-to-location rule, using a procedure that allowed the animal to remain in visual contact with the target site during the very brief delay period. Stage 2 and 3 adapted monkeys incrementally to tolerate visual separation from the target during the brief delay interposed between study and test. Stage 4 exposed monkeys to a slightly longer delay between study and test to prepare them for the performance tests using delay titration. To advance from one stage to the next, monkeys had to choose correctly on 13 of the 16 trials administered on 2 consecutive days (81% accuracy). Monkeys were given a maximum of 10 days of testing in which to meet criterion at each stage.

***Stage 1.*** Three foraging sites were used on each trial. The placement of the sites was randomized across trials to produce trial-unique configurations. During the study phase of each trial, the foraging sites were not covered. Consequently, the monkeys could see the two empty sites indicated by the black bases (weight-lifting plates), and two small pieces of fruit placed at the target site. One of these two pieces of fruit was enclosed in a clear plastic box that allowed the monkey to see but not procure it; thus, a piece of fruit remained after the monkey had visited the site during the study phase. Because the monkeys could see the fruit, they could move directly to the baited target site, without searching. After retrieving the one available piece of fruit, the monkey was returned to the transport cage. The experimenter then covered the two unbaited sites, ensured that the subject was watching, placed a fresh piece of fruit at the target site, and covered it with a flowerpot. The monkey was immediately released and allowed to look in only a single foraging site. If this first look was to the correct location, the monkey was permitted to consume the food reward, but if this first look was to an incorrect location the monkey was not permitted to look in any other sites, and was returned to the transport cage. There was no correction following errors. The intertrial interval (ITI) was ~30 s. Monkeys were given 8 trials each day for 5 or 6 days per week.

***Stage 2.*** The procedure was identical to that in stage 1, except that after the monkey watched the rebaiting of the target site, a tarp blocked the monkeys' view of the foraging sites for ~12 s before it was released to search for the food.

***Stage 3.*** The procedure was identical to that in stage 2, except that the monkeys' view of the sites was blocked before the target site was rebaited and the sites covered. Monkeys still spent ~12 s behind the tarp.

***Stage 4.*** The delay between sample and test phases was increased to 30 s. To prevent the monkeys from using an auditory cue to remind them of the location of the food during the delay, flowerpots were always placed on foraging sites in the same order; the food reward was deposited at the appropriate location during this sequence.

*TABLE 2.*

*Days to Criterion in Experiment 2**

| | Acquisition | | | | Delay titration (min) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Monkey | Stage 1 | Stage 2 | Stage 3 | Stage 4 | 1 | 2 | 3 | 4 | 5 | 10 | 15 | 20 | 25 | 30 |
| Sk | 2 | 2 | 2 | 4 | 2 | 2 | 3 | 5 | 3 | 6 | 5 | 4 | **10** | — |
| Cm | 2 | 2 | 2 | 4 | 2 | 3 | 3 | 6 | 2 | 3 | **10** | — | — | — |
| Cj | 2 | 8 | 10 | 2 | 2 | 7 | 2 | 2 | 2 | 3 | 4 | 8 | 3 | 3 |
| La | 10 | 9 | 6 | 7 | 2 | 2 | 3 | 2 | 5 | 6 | 3 | 7 | 6 | **10** |
| Pl | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 2 | 3 | 3 | 7 | 3 | 3 |
| Mean | 3.6 | 4.6 | 4.4 | 3.8 | 2.0 | 3.2 | 2.6 | 3.6 | 2.8 | 4.2 | 5 | 6.5 | 5.5 | 5.3 |
| Md | 3 | 3 | 2 | 4 | 2 | **10** | — | — | — | — | — | — | — | — |
| Sd | 2 | 2 | 2 | 3 | 2 | **10** | — | — | — | — | — | — | — | — |
| Sm | 2 | 2 | 3 | 2 | 2 | 7 | 3 | 2 | 4 | **10** | — | — | — | — |
| Qq | 2 | 2 | **10** | — | — | — | — | — | — | — | — | — | — | — |
| Ch | 2 | 2 | 2 | 4 | 2 | **10** | — | — | — | — | — | — | — | — |
| Mean | 2.2 | 2.2 | 3.8 | 3.3 | 2 | 9.3 | 3 | 2 | 4 | 10 | — | — | — | — |

*Numerals indicate days required to achieve criterion in each stage of acquisition of the matching-to-location rule (stages 1–4), and at each delay during delay titration. Monkeys were allowed 10 days to meet criterion at a given stage of acquisition or delay. Numerals in bold font indicate that the monkey did not meet criterion during the 10 days allotted. Monkey Qq received an additional 10 days of training at stage 3, but still did not meet criterion (see text). Unoperated control: Sk, Cm, Cj, La, Pl. Selective excitotoxic hippocampal lesions: Md, Sd, Sm, Qq, Ch.

### *Delay Titration*

After acquiring the matching-to-location rule, the monkeys began testing with a series of longer delays (1, 2, 3, 4, 5, 10, 15, 20, 25, and 30 min). For delay conditions up to and including 5 min, three trials were administered each day. For delays of 10 min and longer only 2 trials were given per day. To advance from one delay condition to the next, the monkeys were required to perform accurately in five of the six trials conducted over 2 or 3 consecutive days (83% accuracy), as appropriate for the delay being used. Monkeys were given up to 10 days to meet this criterion at each delay. As during acquisition, monkeys were permitted only one look at test and there was no correction for errors. The ITI was 30 s. The dependent measure was the longest delay at which each monkey could attain criterion.

## Results

Performance improved dramatically following the additional training with the matching-to-location rule at short delays. Except for one monkey in the operated group, all the monkeys were able to achieve criterion (81% accuracy) on stage 4, which required monkeys to match to location after a 30-s delay interposed between study and test phases of a trial. Days to criterion for each monkey at each stage of training are shown in Table 2. The one monkey (Qq) that failed to reach stage 4 did succeed when allowed to see the target site rebaited (stage 2), but could not meet criterion when the target site was rebaited out of view (stage 3). In an effort to overcome this monkey's difficulty, it was given an additional 10 days of testing on stage 3, in which the eight trials were administered in two separate blocks of four trials each day. This monkey still failed to meet criterion and for the delay titration was assigned a score of 0. On the performance tests using the delay titration procedure, control monkeys were able to meet criterion at significantly longer delays than were monkeys with hippocampal lesions (Fig. 5; $t_8 = 5.57$, $P < 0.01$).

Monkey Qq performed worse than any other operated monkey in Experiment 2. Because Qq received NMDA, rather than IBO, injections into the hippocampus, and these injections were made via an occipital rather than a dorsal approach (for details, see

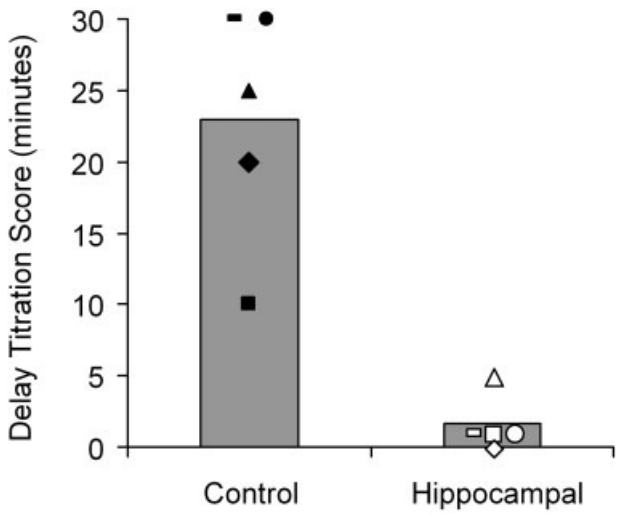


**FIGURE 5. Spatial delayed matching-to-sample after extensive training on the matching rule. The delay was gradually increased each time monkeys met criterion at a given delay. Scores indicate the longest delay at which monkeys maintained criterion accuracy (83%) in Experiment 2. Filled symbols represent monkeys in the control group (Sk, diamond; Cm, square; Cj, circle; La, triangle; Pl, dash), while open symbols represent monkeys in the operated group (Md, circle; Sd, square; Sm, triangle; Qq, diamond; Ch, dash).**

Hampton et al., 2004), there is a possibility that the hippocampal lesion in this monkey differs from those in the other monkeys of the experimental group. Although inspection of the MR scans did not reveal any such differences, there might be a more subtle difference not evident in MRI. Accordingly, we reanalyzed the behavioral data excluding monkey Qq; all statistical results for both Experiments 1 and 2 remain unchanged when this animal is removed from the analyses.

# EXPERIMENT 3

Many animals appear to use an allocentric strategy, or "cognitive map" (O'Keefe and Nadel, 1978) to solve spatial memory tests similar to those used in Experiments 1 and 2. One defining feature of a cognitive map is the ability to navigate to a known goal, using distal landmarks, from a novel start point. To assess whether monkeys in the present experiments used a cognitive map to encode the location of food, we required monkeys to approach the test array from one side of the testing room during study, and from the opposite side of the room at test. If monkeys encode the location of the baited site using allocentric information comprising a "cognitive map," they should be able to accurately relocate the baited site even when they approach it from a different starting point from that used during study.

## Materials and Methods

### *Subjects*

These were the same monkeys that took part in Experiments 1 and 2, with the exception that only 9 of the 10 monkeys were used. Qq, the monkey that could not meet criterion in the acquisition phase of Experiment 2, was excluded, leaving five animals in the control group and four in the hippocampal lesion group.

### *Testing Room*

This is the same testing room used in Experiments 1 and 2. We label the corner of the room from which monkeys were accustomed to starting trials, A, and the opposite side, located just outside the fenced area, B (see Fig. 2). Trial types can thus be described by two letters, the first indicating the side from which the study run was made, and the second indicating the side from which the test run was made. Each of the four possible trial types (AA, AB, BB, and BA) was run once each day in random order. To carry out these tests, monkeys had to be moved in the transport cage between study and test, and therefore required pretraining to adapt to this change in procedure.

### *Pretraining*

Monkeys were allowed to find food in trial-unique arrays consisting of three foraging sites, starting from A, the side of the room used in previous testing. The food was visible during the study phase, as in Experiment 2. After the monkey obtained the food and returned to the transport cage, the cage was covered with a tarp and moved into the fenced area of the testing room normally occupied by the experimenter. The sites were then recovered, the transport cage returned to point A, the tarpaulin removed, and the monkey allowed a single look. Monkeys continued training in this manner until they achieved at least five correct responses over three consecutive sessions of two trials each (i.e., 83% accuracy). At the end of pretraining, they were presumably adapted to being moved between study and test. Four test trials were administered per day, in two sessions of two trials each.

### *Main task*

The study phase of each trial was as in Experiment 2, except that half of the study phases were conducted from point A and the others from B. When the monkey had collected the piece of fruit from the target site and returned to the transport cage, the cage was immediately covered with the tarp and the monkey moved into the small fenced area. The target site was rebaited and all sites covered. The monkey was then moved to the appropriate test location for that trial (A or B). After 1 min had elapsed from the time the cage was first covered, it was uncovered, and the monkey was allowed one look to find the hidden food. Four trials were run per day, two in each of two different sessions. Testing was continued for 12 days, yielding a total of 48 trials. Thus, there were 12 trials of each type (AA, AB, BB, BA), administered in random order with the constraint that one trial of each type was used each day. Half the trials were Same trials, on which study and test phases of the trial started from the same location, the other half were Switch trials, on which study and test phases were conducted from opposite sides of the array.

## Results

A repeated-measures ANOVA on the arcsine-transformed scores revealed a significant main effect of trial type; there was no significant group difference or group $\times$ trial interaction (Fig. 6; trial type: $F_{1,7} = 69.01$, $P < 0.01$; Group: $F_{1,7} = 0.58$; Group $\times$ trial type: $F_{1,1} = 0.05$). Considered together, the nine monkeys were correct on 85% of Same trials and 45% of Switch trials. Performance on Switch trials was better than expected by chance (33.3%), as shown by a one-sample *t*-test (mean = 45%, $t_8 = 2.41$, $P < 0.05$).

# EXPERIMENT 4

In Experiment 3, the monkeys made many mistakes when required to relocate the baited location starting from the opposite side of the room from that used during the study phase of the trial. Above chance performance on the Switch trials demonstrated that the monkeys did use a "cognitive map" or allocentric strategy to some degree. In Experiment 4, we sought to determine whether the many mistakes were due to use of a response or egocentric strategy as well (e.g., Benhamou and Poucet, 1996; Packard, 1999), or perhaps were due to confusion about which strategy should be used. That is, even though the monkeys demonstrated some use of an allocentric strategy, it was still a logical possibility that the errors committed on Switch trials were unevenly distributed between the two remaining sites. To determine whether errors made in Exper-

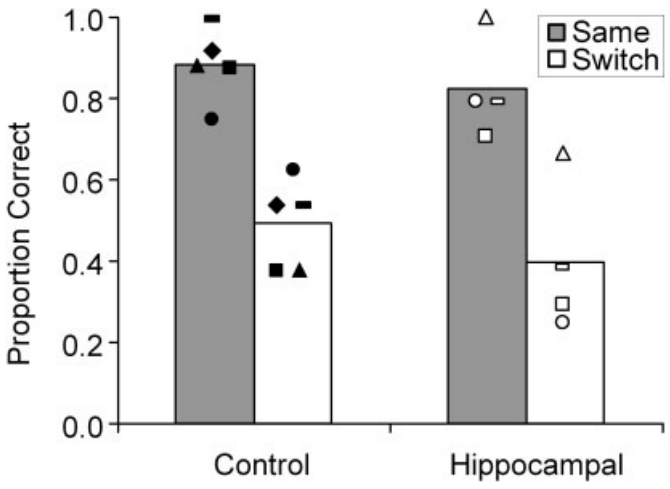


**FIGURE 6. Spatial matching accuracy from a different starting location than that used during study (Experiment 3). Same: trials in which monkeys approached the array of foraging blocks from the same location at study and at test. Switch: trials in which monkeys approached the array from the opposite sides of the room during study and test. Chance performance is 33%. Filled symbols represent monkeys in the control group (Sk, diamond; Cm, square; Cj, circle; La, triangle; Pl, dash), while open symbols represent monkeys in the operated group (Md, circle; Sd, square; Sm, triangle; Qq, diamond; Ch, dash).**

iment 3 could be due to use of an egocentric strategy, as opposed to random errors, we presented monkeys with symmetrical arrays on Switch trials. Because these arrays look the same from either side, Switch trials pit egocentric and allocentric responses against each other. Monkeys might respond to location in the room (allocentric cognitive map) or to location relative to the monkey's current position (egocentric response rule). Thus, a monkey using an egocentric strategy to relocate baited sites at test would make reflection errors on Switch trials. For example, if the monkey saw a horizontal array of three sites at study, and the site to the monkey's right was baited, he would choose the rightmost site when approaching the array from the opposite side, erring by choosing the wrong end of the array. In contrast, if errors made in Experiment 3 simply reflect poor implementation of the cognitive map strategy, monkeys would be equally likely to make an error by choosing the middle site in the array as to choose the incorrect end of the array. We therefore evaluated, for those errors committed on Switch trials, whether reflection errors occurred more frequently than errors to the middle position.

## Materials and Methods

### *Subjects*

These were the same monkeys that took part in Experiment 3.

### *Testing Room*

This is the same testing room used in Experiments 1, 2, and 3.

### *Main Task*

No additional training was provided. Each monkey participated in 60 trials, half of which were Same trials, and half of which were Switch trials. Same trials were conducted exactly as in Experiment 3. Switch trials differed from those in Experiment 3 only in that symmetrical arrays (i.e., arrays that looked the same from either side) were used. The arrays used on Switch trials formed a horizontal line, a forward or backward "slash," or a vertical line. A "plus" configuration was also used, but due to technical errors during testing, this configuration could not be included in the analysis. Each symmetrical array was used on a randomly distributed six trials intermixed with Same trials, with each of the three sites in a given array serving as the baited target twice. Thus, 24 Switch trials, and 30 Same trials for each monkey were available for the analysis of overall percent correct on the two types of trials. This analysis is the same as that performed in Experiment 3. The main purpose of the current experiment was to analyze errors on Switch trials, and this placed a further constraint on the data available for analysis. Trials on which the central site in the array was correct were excluded from analysis, because no egocentric error is possible on these trials. Thus, for the analysis of errors on Switch trials a total of 16 trials was available for each monkey.

## Results

Accuracy on Same and Switch trials was similar to that observed in Experiment 3. Both groups performed less well on Switch than on Same trials (Fig. 7; trial type: $F_{1,7} = 87.81$, $P < 0.01$; Group: $F_{1,7} = 0.31$; Group × trial type: $F_{1,1} = 0.10$), and overall performance was better than chance on Switch trials (mean = 45%, $t_8 = 2.44$, $P < 0.05$). Most pertinent to the current experiment, neither group of monkeys made more egocentric errors than the 50% expected by chance (Controls: mean = 55%, $t_4 = 0.89$; Hp: mean = 45% , $t_3 = 1.26$).

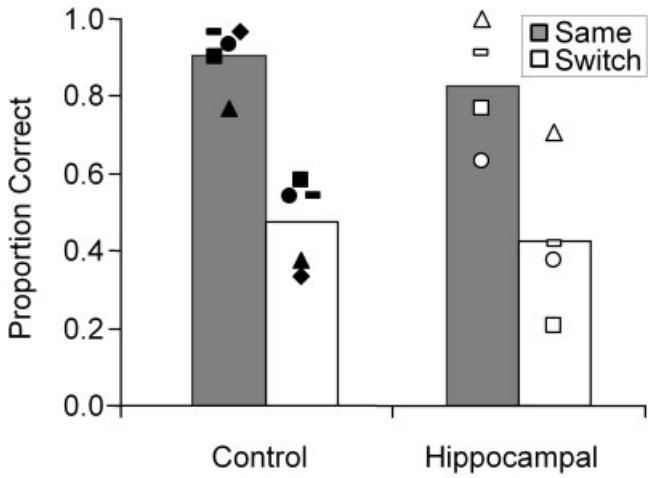


**FIGURE 7. Spatial matching accuracy assessed with symmetrical array probe trials (Experiment 4). Same trials were conducted as in Experiment 3, using trial-unique arrays. In Switch trials, symmetrical arrays were used such that monkeys could search in either the location in the room where they had found food during study (allocentric response), or could move from the starting location in the same direction as they had during study (egocentric response). Chance performance is 33%. Filled symbols represent monkeys in the control group (Sk, diamond; Cm, square; Cj, circle; La, triangle; Pl, dash), while open symbols represent monkeys in the operated group (Md, circle; Sd, square; Sm, triangle; Qq, diamond; Ch, dash).**

## DISCUSSION

The results of Experiments 1 and 2 demonstrate for the first time that selective hippocampal lesions impair memory for location in an open-field test in monkeys. This result highlights the conservation of a spatial memory function of the hippocampus across a wide range of taxa. Although performance was attenuated in Experiments 3 and 4 when monkeys were required to navigate from a position different than the one used during the study phase of a trial, accuracy remained significantly above chance. This ability to navigate to the goal using a different route is indicative of an allocentric representation ("cognitive map") of the location of the goal. Complementing this evidence for allocentric representation, probe trials in Experiment 4 found no evidence that the monkeys used an egocentric or response strategy. In Experiment 2 control monkeys remembered the goal location significantly longer than did operated monkeys, despite the fact that 4 of the 5 operated monkeys performed well at the shortest delay. Selective hippocampal lesions therefore appear to impair the ability of monkeys to retain information specifying the goal location. The rapid forgetting observed here reinforces earlier findings in which fornix transection in monkeys also impaired retention of spatial information in a large T-maze (Murray et al., 1989).

### Large-Scale Versus Small-Scale Environments

Previously published data regarding the contribution of the hippocampus to spatial memory in primates has been equivocal. In humans, there is considerable evidence that the hippocampus is involved in spatial memory, coming from both neuropsychological studies (Bohbot et al., 1998; Kessels et al., 2001), and functional imaging studies (Maguire et al., 1997, 1998; Grön et al., 2000). Additionally, electrophysiological studies in monkeys have identified hippocampal neurons with properties that could support spatial navigation (Nishijo et al., 1997; Rolls, 1999). However, most studies of spatial memory following selective hippocampal lesions in monkeys, in which cortex surrounding the hippocampus was intact, have found no deficits. For example, selective hippocampal lesions failed to yield deficits on spatial reversal learning (Ridley et al., 1997; Murray et al., 1998) (Experiment 1) and object-place association (Málková and Mishkin, 2003), even though earlier studies based on aspirative lesions of the hippocampus, which include the underlying parahippocampal cortex, found impairments on the same tasks (Mahut, 1971; Jones and Mishkin, 1972; Parkinson et al., 1988). These negative findings involved small-scale environments in which monkeys responded by reaching, rather than by traveling to, different locations in space. Locomotion is a conspicuous feature of hippocampal-dependent spatial memory tests typically conducted with rodents, such as the Morris water maze (Morris, 1984) and the radial-arm maze (Olton and Papas, 1979). Consequently, it is tempting to speculate that the absence of large-scale locomotion in tests used with monkeys is responsible for previous failures to observe deficits in spatial memory following selective hippocampal damage (Ridley et al., 1997; Murray and Mishkin, 1998; Murray et al., 1998, Experiment 1; Málková and Mishkin, 2003). At least two sets of findings, however, are inconsistent with this idea. Murray et al. (1998) (Experiment 2), and Beason-Held et al. (1999) (delayed recognition span task, spatial condition) did report impairments in spatial tasks in monkeys with selective hippocampal lesions, and these tasks did not involve locomotion. In the first case the test used was "spatial scenes" (Gaffan, 1994). In this test, monkeys are required to learn which of two small dots on a monitor screen, when touched, leads to reward delivery. The two dots are always embedded in a particular background or scene, consisting of several large geometric shapes that maintain a consistent relationship to the rewarded dot across trials. Also, three ASCII characters appear in the "foreground" and could serve as additional landmarks. Thus the location of the rewarded dot can be encoded with respect to the various foreground objects and background shapes making up the scene. In this way, the appearance of the scene may model a real spatial context, in effect constituting virtual locomotion. Alternatively, the scenes task may engage memory functions other than spatial memory that also depend on an intact hippocampus, such as episodic-like memory (e.g., Gaffan, 1994).

In the case of the other positive finding, Beason-Held et al. (1999) used a spatial span task. Each trial began with presentation of a single rewarded location marked by a brown disk on a small 18-well test tray placed before the monkey. The monkey was allowed to displace the disk to retrieve the food reward hidden underneath it. Next, two identical disks were presented, one at the previously rewarded location and another at a novel location. The monkey was required to displace the disk at the new location to obtain another food reward. On each subsequent presentation of the test tray, an additional location was added to the list. This was repeated until the monkey erred by choosing a previously rewarded location. The number of correct responses made before the error constituted the monkey's spatial memory span on that trial. It is not clear how a deficit in this task relates to the failure to find deficits in similar spatial tasks, but the use of memory span stands out as a unique feature of this task.

The results with spatial scenes (Murray et al., 1998) and spatial span (Beason-Held et al., 1999) show that large-scale locomotion is not required to yield deficits in spatial memory after selective hippocampal damage. Nevertheless, the fact that reliable deficits in spatial memory were observed following selective hippocampal lesions in the present study, but not in several other studies using small-scale environments, does suggest that there is something cognitively different between open-field testing and typical nonhuman primate spatial memory tests using small scale spatial layouts (for a similar argument applied to human imaging studies, see Maguire et al., 1997).

In at least one case, a type of spatial memory that was not dependent on the hippocampus was found to depend on the adjacent parahippocampal cortex. In small-scale spatial tests, selective hippocampal lesions did not impair memory for either one trial object-place associations, or memory for locations, while lesions of posterior parahippocampal cortex did impair performance in both tasks (Málková and Mishkin, 2003). Consistent with the importance of parahippocampal cortex in these tasks, imaging studies of humans also implicate parahippocampal cortex in processing the layout of scenes (Maguire et al., 1997; Aguirre et al., 1998; Epstein et al., 1999), but not in planning routes or navigation per se (Maguire et al., 1997; Epstein et al., 1999; Burgess et al., 2002).

This raises the possibility that parahippocampal cortex supports memory for scenes or landmarks, whereas the hippocampus is critical for remembering movement in relation to the scene or landmark (Maguire et al., 1997; Burgess et al., 2002), a possibility that invites empirical investigation.

### Cognitive Mapping

Recent studies suggest that the hippocampal role in navigation may not be exclusively one of supporting "cognitive mapping" as traditionally conceived. For example, rats with fornix transection are impaired in relocating a refuge using self-movement (dead reckoning), when they must navigate in the dark without landmarks (Whishaw et al., 2001). In addition, although lizards with dorsomedial cortex lesions are impaired on a spatial memory task, they do not appear to navigate using landmarks in the test arena (Day et al., 2001). Finally, a novel stringent test for cognitive mapping indicates that the concept may be in need of clarification (Benhamou, 1996). In this test, rats were unable to navigate to a hidden goal using a novel partial view of a familiar array of landmarks. In contrast, navigation was accurate when the rats had access to a partial view they had been trained with, indicating that they did not integrate different views into a single map-like representation. Humans tested under similar conditions also fail to report use of an integrated map (Gibson, 2001). Recent electrophysiological studies in monkeys indicate that hippocampal neurons do not encode locations, as generally conceived in cognitive mapping. Whereas CA3 and CA1 neurons in rats often appear to code locations ("place cells"), neurons in monkeys may encode particular views of the external world that do not specify an animal's location in the world (Rolls, 1999). Even though the present data indicate that the monkeys encoded some allocentric information about the goal locations, we cannot determine whether our monkeys were using a true "cognitive map" (Gibson, 2001). Tests involving rotation of allocentric landmarks, which we did not carry out, would be required to provide direct evidence for the use of such cues. Nonetheless, the probe trials of Experiment 4 do appear to rule out use of response or egocentric information. It should be noted that more general accounts of hippocampal function that do not invoke cognitive mapping may be adequate to account for the role of the hippocampus in spatial memory (e.g., Wise and Murray, 1999; Eichenbaum et al., 1999).

### Foraging and Spatial Memory

One objective of these experiments was to test whether a more natural foraging task might more readily engage spatial memory, and reveal memory deficits, than do traditional tests used with nonhuman primates. The poor performance observed in Experiment 1, and the remarkable improvement following explicit training in the matching rule in Experiment 2 indicate that, even in this open-field setting where a large food resource remains in place between study and test, laboratory macaque monkeys require explicit training to achieve high levels of matching-to-location performance. Indeed, the low level of spontaneous matching shown here is reminiscent of the T-maze nonmatching behavior reported by Murray et al. (1989). Nonetheless, after acquiring the matching-to-location rule, control monkeys met criterion at a mean delay of 23 min, which is considerably longer than the delays used in the typical studies of spatial memory in monkeys discussed in the present study.

## CONCLUSIONS

The present results emphasize the importance of the hippocampus for retention of spatial information in monkeys, and provide additional support for the idea that spatial information processing by the hippocampus arose early in vertebrate evolution and has been conserved (Rodríguez et al., 2002a). Because we have not investigated other types of memory (e.g., nonspatial visual memory, episodic-like memory) we make no claims about the potential contribution of the hippocampus in these other domains. However, we acknowledge the evidence for hippocampal contributions to episodic memory in humans (e.g., Vargha-Khadem et al., 1997) and to memory with episodic properties in nonhuman animals (e.g., Gaffan, 1994; Kesner et al., 2002; Fortin et al., 2002). Whether spatial memory is an exemplar of a more general type of memory served by the hippocampus in monkeys remains to be elucidated. If so, perhaps the ancient vertebrate hippocampus played roles in other forms of memory. Or perhaps new functions for the hippocampus, consistent with its spatial coding function, have arisen in select species. What is clear is that monkeys, like their ancient vertebrate ancestors, depend on the hippocampus to know where they are and where they need to be.

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