Nonnavigational spatial memory performance is unaffected by hippocampal damage in monkeys

Benjamin M. Basile1 | Robert R. Hampton2

1Section on the Neurobiology of Learning and Memory, Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, Maryland
2Department of Psychology and Yerkes National Primate Research Center, Emory University, Atlanta, Georgia

Correspondence
Benjamin M. Basile, Laboratory of Neuropsychology, NIMH, Building 49, Room 1880, 49 Convent Drive, Bethesda, MD 20892-4415.
Email: benjamin.basile@nih.gov

Funding information
National Institute of Mental Health, Grant/Award Numbers: ZIAMH002887, R01MH082819; National Science Foundation, Grant/Award Numbers: BCS-1632477, IOS-1146316, BCS-0745573

Abstract
Evidence that the hippocampus is critical for spatial memory in nonnavigational tests is mixed. A recent study reported that temporary hippocampal inactivation impaired spatial memory in the nonnavigational Hamilton Search Task in monkeys. However, several studies have documented no impairment on other nonnavigational spatial memory tests following permanent hippocampal lesions. It was hypothesized that transient, but not permanent, hippocampal disruption produces deficits because monkeys undergoing transient inactivation continue to try to use a hippocampal-dependent strategy, whereas monkeys with permanent lesions use a nonhippocampal-dependent strategy. We evaluated this hypothesis by testing five rhesus monkeys with hippocampal lesions and five controls on a computerized analogue of the Hamilton Search Task. On each trial, monkeys saw an array of squares on a touchscreen, each of which "hid" one reward. Retrieving a reward depleted that location and monkeys continued selecting squares until they found all rewards. The optimal strategy is to remember chosen locations and choose each square once. Unlike the inactivation study, monkeys with hippocampal damage were as accurate as controls regardless of retention interval. Critically, we found no evidence that the groups used different strategies, as measured by learning rates, spatial search biases, perseverative win-stay errors, or inter-choice distance. This discrepancy between the effect of inactivations and lesions may result from off-target effects of inactivations or as-yet-untidentified differences between the physical and computerized tasks. Combined with previous evidence that hippocampal damage impairs navigational memory in monkeys, this evidence constrains the role of the hippocampus in spatial memory as being critical for navigational tests that likely involve allocentric spatial memory but not nonnavigational tests that likely involve egocentric spatial memory.

KEYWORDS
allocentric, egocentric, nonhuman primate, rhesus, self-ordered search, temporal lobe

1 | INTRODUCTION

Hippocampal function is broadly conserved across many species and robust evidence indicates it is critical for some types of spatial memory (e.g., Hampton & Shettleworth, 1996; Jarrard, 1993; Sherry et al., 1992). Most evidence comes from small vertebrates navigating around larger environments and less is known about the role of the hippocampus in types of spatial memory that do not involve navigation. One prominent theory is that the hippocampus is critical for allocentric (landmark-guided) but not egocentric (self-oriented) spatial memory, and that navigation primarily taxes allocentric coding (e.g., Holdstock et al., 2000; Lavenex & Lavenex, 2009; Packard & McGaugh, 1996). In nonhuman primates, there is good but sparse evidence that the hippocampus is necessary for navigational tasks (Glavis-Bloom et al., 2013; Hampton, Hampstead, et al., 2004; Lavenex et al., 2006). In contrast, evidence for the role of the primate hippocampus in nonnavigational spatial tasks is less consistent. Although some studies report that hippocampectomized monkeys have difficulty remembering locations (e.g., Beason-Held et al., 1999), most show that they remember locations normally, show deficits that resolve during development, or only show deficits in remembering object-location combinations (e.g., Bachevalier & Nemanic, 2008; Blue...
et al., 2013; Heuer & Bachevalier, 2011; Malkova & Mishkin, 2003; Murray & Mishkin, 1998). Thus, evidence for the role of the primate hippocampus in nonnavigational spatial tasks that likely rely on egocentric memory is mixed or negative.

A recent study using temporary inactivations concluded that the hippocampus is critical for nonnavigational spatial memory (Forcelli et al., 2014). Four monkeys performed the Hamilton Search Task, in which eight pieces of food were hidden in eight boxes arranged in a row from left to right. The monkeys chose repeatedly until they had retrieved all food. Like the radial maze used with rodents, the optimal strategy is to remember all visited locations and visit each location only once (e.g., Suzuki et al., 1980). Unlike the radial maze, the monkeys do not navigate through space using landmarks but instead reach over short distances from a single position. Temporary pharmacological inactivation targeting a patch of tissue within the hippocampus impaired memory when choices were separated by a 30-s retention interval, but not when separated by a 1-s interval and thus presumably could be remembered via working memory or short-term memory, or when the boxes could be remembered via nonspatial color cues. The authors argued that the hippocampus is involved in nonnavigational spatial memory and hypothesized that previous studies did not show impairments because monkeys with permanent lesions compensate for the lack of hippocampi by solving spatial tasks using a different, but unspecified, strategy than that used by normal monkeys.

The conclusion of the inactivation study is based on two assumptions that have not been directly evaluated: (a) monkeys with permanent hippocampal damage will perform well on the Hamilton Search Task and (b) they will use a different search strategy than intact monkeys. Here, we evaluated these assumptions by testing five rhesus monkeys with selective, bilateral, fiber-sparing hippocampal lesions, and five unoperated control monkeys on a computerized analogue of the Hamilton Search Task. On each trial, monkeys saw an array of locations on a touchscreen, each of which would only be rewarded the first time it was selected (Figure 1a). As in the Hamilton Search Task, the optimal strategy is to remember all selected locations and choose each location only once per trial. We first assessed learning to a set criterion with increasing numbers of locations, then performance with eight locations and 1- or 30-s retention intervals, paralleling the inactivation study (Forcelli et al., 2014). We evaluated several metrics that might be diagnostic of differences in strategy, including learning rate, spatial search bias, inter-choice distance, and perseverative win-stay choices. If the hippocampus is critical for spatial memory in this nonnavigational test, then hippocamprectomized monkeys should perform less accurately or with a different strategy than controls, particularly at the longer retention interval. Conversely, if the hippocampus is not necessary for spatial memory in this nonnavigational test, then accuracy and strategy metrics should be equivalent between the two groups.

2 | METHODS

2.1 | Subjects

We tested 10 adult male rhesus monkeys (mean age at start of testing: 11.26 years) in their home cages. Five monkeys had bilateral excitotoxic lesions of the hippocampus and five were unoperated controls. Whenever possible, monkeys were pair-housed when not testing. Pair-housed monkeys were separated during testing by a protected-contact divider that allowed them limited visual, auditory, and tactile access to their partner but not their partner’s computer screen. Monkeys received full food rations after each day’s testing, and water was available ad lib. All monkeys had prior experience with touchscreen-based cognitive tasks (Basile & Hampton, 2010, 2011, 2013a, 2013b, 2013c, 2017; Gazes et al., 2012; Templer & Hampton, 2012). All procedures complied with US law and the National Institutes of Health guide for the care and use of laboratory animals.
2.2 | Apparatus

We tested subjects 6 days a week using portable testing rigs equipped with a 15” color LCD touch screen (3 M, St. Paul, MN; and ELO, Milpitas, CA) running at a resolution of 1,024 × 768 pixels, stereo speakers, and two automatic food dispensers (Med Associates Inc., St. Albans, VT) which dispensed nutritionally-complete food pellets into cups below the screen. Testing equipment was available to the monkeys ~7 hr a day.

2.3 | Surgery

The procedures we used to make selective excitotoxic lesions of the hippocampus have been previously described (Hampton, Buckmaster et al., 2004). Briefly, we plotted a string of targets along the anterior–posterior axis of the hippocampus for each hemisphere based on T1-weighted magnetic resonance (MR) scans of each monkey. Injection sites were adapted to each hemisphere and comprised eight or nine sites separated by ~2 mm. Prior to surgery, monkeys were anesthetized using a mixture of dexmedetomidine (0.02 mg/kg) and low-dose ketamine (5 mg/kg) and maintained on isoflurane gas (1%–4% to effect). Once under gas anesthesia, dexmedetomidine was reversed. The monkeys were monitored throughout surgery. Using aseptic procedures, we opened a small incision (~2–3 cm) in anatomical layers on the top of the skull and drilled a small hole to visualize the central sinus for purposes of adjusting medial-lateral position of the injection tracks. We then opened a second incision on the back of the skull, just superior to the occipital ridge, retracted the temporalis muscles, and drilled two small entry holes in line with our two injection paths. We inserted both needles to the most anterior injection sites, injected 2 μL of NMDA (62.5 mg/mL; 0.42 M) at .25 μL/min, waited 3 min for the excitotoxin to diffuse, retracted the needles 2 mm to the next site, and repeated until we reached the most posterior site. We then waited five additional minutes before withdrawing the needle from the brain. Finally, we closed all incisions in anatomical layers. Postsurgical seizures were managed with diazepam (0.5 mg/kg) as needed. Pain and infection risk were managed with a regimen of flunixin (1 mg/kg) and ceftriaxone (25 mg/kg) as directed by veterinary staff.

2.4 | Lesion assessment

Hippocampal damage can be estimated in vivo via magnetic resonance imaging (MRI; Málková, Lex, Mishkin, & Saunders, 2001; Nemanic et al., 2002). We assessed estimated damage using the formula published by Málková et al. (2001) as described previously (Hampton, Buckmaster et al., 2004). Six or seven days after surgery, each monkey received a T2-weighted MR scan to visualize the edema that indicates cell death (Figure 1b). For monkeys in which this T2 scan indicated that less than half of the hippocampus was directly impacted by the injections, we proceeded with a second surgery targeting the remaining tissue. Approximately 150 days post-surgery when atrophy has completed, we acquired a post-operative T1-weighted scan, traced in ImageJ (Schneider et al., 2012) the area of the shrunken hippocampus on sequential coronal sections separated by 1 mm in the AP plane, and summed these sections to quantify the volume of the remaining hippocampal tissue. For tracing, we included all subfields of the hippocampus as well as the subiculum. Each hemisphere was traced four times per tracing session to give an average volume, each session was repeated three times during different sittings and without reference to the previous tracing sessions, and the final measure used in analyses was the mean of these three sessions to provide an average that corrected for individual hand jitter in an individual tracing. We then compared that post-operative volume to the volume of the hippocampus from pre-surgical MR images traced in the same way (Figure 1b), and used a regression function based on a comparison of MR-observed shrinkage to histological material to calculate the estimated actual damage (Hampton, Buckmaster et al., 2004; Málková et al., 2001). The estimated damage is presented in Table 1. Damage in this group was more complete than several previous studies of hippocampal lesions in monkeys (see Hampton et al., 2004, Table 1) and was similar to the amount of damage that successfully causes memory impairment in navigational tasks (Hampton, Hampstead, et al., 2004). Most importantly, our lesions included the area inactivated in the previous study of nonnavigational spatial memory (compare Figure 1b to figure 1c.d of Forcelli et al., 2014).

2.5 | Experimental design

2.5.1 | Assessment of learning and memory span

On each trial, monkeys had to find all the red dots hidden in an array of possible screen locations (Figure 1a). Monkeys started each trial by

<table>
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<tr>
<th>Monkey</th>
<th>Surgeries</th>
<th>Percentage of volume reductiona</th>
<th>Percentage of estimated damageb</th>
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<td>Left</td>
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| a (1 - [postoperative volume/preoperative volume]) × 100. |
| b Calculated based on Málková et al. (2001) and Hampton et al. (2004). |
| c Calculated from total hippocampal volume (i.e., left volume + right volume). |
touching a green start square. A number of red dots (120 × 120 pixels), each worth one piece of food, were briefly flashed on the screen for 0.5 s and then immediately covered by white squares (150 × 150 pixels). The screen locations were drawn randomly from a possible 24, and the same locations were maintained throughout the trial until the monkey had located all red dots. If the monkey chose a white square that it had not already chosen this trial, the square disappeared revealing one of the red dots, and the monkey earned food by touching the red dot. If the monkey chose a white square that it had already chosen earlier in the trial, the square disappeared revealing nothing. After each choice and the following interstimulus interval (ISI), all of the white squares used on that trial reappeared for another retrieval attempt. Thus, the optimal strategy was to remember all chosen locations and only choose each location once per trial (i.e., number of choices to retrieve all food = number of locations).

During training, the ISI between choice opportunities within a trial was 1 s. To discourage the monkeys from "cheating" by using postural mediation or keeping their hands on a recently-chosen location, the ISI timer reset if the monkey touched the screen during the ISI. Trials ended when the monkey had located all red dots. Trials were separated by a black 20-s interval, and then a new array of locations was presented on the next trial.

The assessment of learning began with two locations per trial. Monkeys completed 200-trial sessions. If a monkey completed 85% or more of the trials in a session without an error (i.e., number of choices to retrieve all food in a trial = number of locations in a trial), then the number of locations presented on each trial was increased by one for the next session. Thus, for learning, a trial with one or more incorrect choices was scored as an error, but making more than one incorrect choice in a given trial did not further count against the criterion and monkeys did have to continue the trial until they had located all the red dots. The assessment of learning ended when the monkey had completed 20 consecutive sessions without increasing the number of locations any further. The number of locations used in this final stage was the memory span for that monkey under these testing conditions. Note that this number is used here to compare our experimental and control groups to each other and different absolute memory span values would be achieved with a different accuracy criterion.

2.5.2 Assesment of criterial performance at a memory load of eight targets

We tested monkeys' spatial memory with an array of eight locations in two 100-trial sessions, one with a 1-s interval between choice attempts and one with a 30-s interval between choice attempts (Figure 1a). This final stage of the experiment paralleled the critical conditions in the inactivation study (Forcelli et al., 2014). The eight screen locations for each trial were drawn randomly from a possible 24, and the same locations were maintained throughout the trial until the monkey had located all red dots. Otherwise, trials proceeded as during learning. Our measures of accuracy were the proportion correct as a function of retrieval attempt (number of red dots found on retrieval attempt X / number of trials) and number of correct choices in the first eight attempts. For number of correct choices in the first eight attempts, chance was determined via Monte Carlo simulation to be 5.3, as in Forcelli et al., (2014).

2.5.3 Evaluation of strategy differences

The authors of the inactivation study did not specify which alternative strategy monkeys with permanent hippocampal damage would use to solve nonnavigational memory tests at a normal accuracy. In the absence of a specific proposal, we evaluated four metrics that might be diagnostic of different strategies or information-processing biases that monkeys might use in this task. First, hippocampal damage might bias monkeys to learn the task via a more slowly acquired habit-based strategy. Thus, we assessed learning rates at different memory loads. Second, hippocampal damage might bias monkeys to use a systematic egocentric response pattern, such as always moving from left to right. Thus, we compared whether the two groups differed in the systematicity with which they sequentially chose screen locations. Third, a bias toward using an egocentric response strategy might manifest itself as a systematic nearest-neighbor travel path from location to location, regardless of absolute start location on the screen. Thus, we assessed the inter-choice distance to test whether monkeys with hippocampal damage were more likely to prioritize proximate or distal targets. Fourth, previous work with rats suggests that hippocampal damage impairs win-shift learning but leaves win-stay learning intact (e.g., McDonald & White, 1993). Although a bias toward win-stay responding is unlikely to be an effective strategy to compensate for poor spatial memory, it nevertheless remains a possible way that monkeys might process information in this task following hippocampal damage. It is even possible that both groups of monkeys might show the same error rate, but with a higher proportion of errors directed to the just-rewarded screen location in the hippocampectomized monkeys. Thus, we evaluated whether monkeys with hippocampal damage showed particular difficulty inhibiting win-stay responses to a just-rewarded location.

2.5.4 Statistical analysis

We tested for lesion effects in accuracy and errors using a combination of paired t tests and repeated-measures ANOVA, as appropriate. Correlations were two-sample Pearson's tests. We compared reaction time distributions using two-sample Kolmogorov–Smirnov tests on Vincentized group distributions, a standard method in reaction time analysis to create group reaction time distributions that maintain the properties of the individual subjects' distributions (Whelan, 2008). All tests were two tailed with α = .05. Effect sizes are partial η² for ANOVA and Cohen's d for t tests (Hurlburt, 2006). We arc sine transformed all proportions prior to statistical analysis to better approximate normality (Aron & Aron, 1999).

3 RESULTS

Hippocampal damage did not reduce memory span or slow acquisition. Monkeys with hippocampal damage and control monkeys did not differ in the memory span they achieved during training (mean: HP = 4.4, C = 3.8; median = 4 for both groups; t8 = 1.09, p = .305). The monkey that progressed to the longest memory span (6) was in the hippocampal
group (Table 1). The groups did not differ significantly in the number of trials to reach criteria with two or three locations (the only phases that all monkeys reached; mean (SD) for two locations: control = 743.2 (362.9), hippocampus = 1,241.4 (447.1); t8 = 1.93, p = .089; for three locations: control = 2,316.6 (1,583.9), hippocampus = 1,290.6 (709.5); t8 = −1.32, p = .223), or in their tendency to make perseverative win-stay errors to the most recently rewarded square (mean (SEM) for three locations: control = 0.45 (0.02), hippocampus = 0.44 (0.02); t8 = −0.33, p = .752; at terminal memory span: control = 0.30 (0.06), hippocampus = 0.18 (0.02); t8 = −1.82, p = .106).

During final testing with eight locations, the groups again performed with similar accuracy. Individually, all monkeys performed above chance at both 1 and 30 s ISI (Figure 1b,e; one-sample t tests of number of correct choices in the first eight attempts against chance for the 100 trials from each retention interval for each monkey: all t99 > 2.54, all p < .013) except for one control monkey in the 1-s retention interval (t99 = −0.36, p = .718). As expected of a test of memory, the longer retention interval resulted in poorer performance, consistent with forgetting. Accuracy was significantly worse at the 30-s retention interval than the 1-s retention interval (Figure 2b,e; main effect of retention interval on number of correct choices in the first eight attempts: F[1,8] = 30.50, p < .001, partial η2 = 0.792). Note that the number of correct choices in the first eight attempts made by our monkeys was completely overlapping with that of the monkeys in the baseline condition of the inactivation study (compare our Figure 2b,e to Figure 2b of Forcelli et al., 2014, in which the control monkeys averaged 6.1 correct). However, hippocampal damage did not reduce accuracy measured across sequential choices (Figure 2a,d; 1-s retention: main effect of group, F(1,8) = 3.32, p = .106, group × attempt interaction, F(7,56) = 1.60, p = .155; 30-s retention: main effect of group, F(1,8) = 0.43, p = .531, group × attempt interaction, F(7,56) = 0.75, p = .634) or as the overall number of locations chosen correctly in the first eight choices (Figure 2b,e; 1-s retention: t8 = 1.83, p = .104; 30-s retention: t8 = 0.58, p = .575). Excluding the one control monkey who performed poorly at the 1-s interval did not produce significant group differences. Further, the overall accuracy of the hippocampectomized monkeys was not correlated with their lesion extent at either retention interval (1-s retention: r3 = .39, p = .512; 30-s retention: r3 = .13, p = .829).

Consistent with findings linking hippocampal damage to hyperactivity (e.g., Abela et al., 2013; Machado & Bachevalier, 2006; Sams-Dodd et al., 1997), the monkeys with hippocampal damage were quicker to make their choices than were the control monkeys (Figure 2c,f). The response time distributions of the two groups differed with both the 1 and 30-s retention intervals (Kolmogorov–Smirnov test; 1-s interval: D = 0.22, p = .013; 30-s interval: D = 0.19, p = .047). The median response times of the hippocampal group were lower for both retention intervals, although that difference only

**FIGURE 2** Selective hippocampal damage did not impair memory on a nonnavigational spatial test. (a) Mean proportion correct as a function of retrieval attempt for control monkeys (C; gray triangles) and monkeys with hippocampal damage (H; red circles) with the 30-s retention interval. (b) Mean number correct in the first eight retrieval attempts for each individual monkey with the 30-s retention interval. (c) Median choice latency on correct trials as a function of retrieval attempt with the 30-s retention interval. Inset shows histogram of all choice latencies for each group. (d-f) As above but with the 1-s retention interval. All error bars are ±SEM [Color figure can be viewed at wileyonlinelibrary.com]
reached statistical significance for the 1-s interval (1-s interval: 453 ms faster; \(t_8 = 4.51, p = .002, d = 2.85\); 30-s interval: 602 ms faster; \(t_8 = 1.19, p = .267, d = 0.75\)). The lack of significance at the 30-s retention interval was due to a single individual, as four of the five monkeys with hippocampal damage had median response times below all of the control monkeys.

To evaluate whether permanent hippocampal damage resulted in a shift in strategy we compared several parameters of performance between hippocampectomized and control monkeys. We found no reliable difference between hippocampectomized and control monkeys. All monkeys showed an initial spatial bias to choose a square near the bottom center of the screen on the first choice (Figure 3a,d); however, this tendency did not differ between groups. This spatial distribution of searches paralleled the results from the inactivation study, in which monkeys started near the middle of the search locations and worked outward (Forcelli et al., 2014). On subsequent choices, neither group showed consistent biases to favor other screen locations. Individual monkeys did show reliable spatial selection patterns for their initial few choices, similar to the trap-lining seen sometimes in studies of foraging (Collett et al., 2013). However, these patterns were observed in individuals from both groups. An analysis of inter-choice distance, similar to analyses of travel distance in foraging studies, showed that inter-choice distance did vary as a function of retrieval attempt but that there was no reliable group difference in tendency to prioritize proximate or distal locations (Figure 3b,e; 1-s interval: main effect of retrieval attempt \(F_{(6,48)} = 2.36, p = .044, \text{partial } \eta^2 = 0.23\), main effect of group \(F_{(1,8)} = 0.21, p = .661\), group \(\times\) retrieval attempt interaction \(F_{(6,48)} = 0.80, p = .572\); 30-s interval: main effect of retrieval attempt \(F_{(6,48)} = 2.62, p = .028\), partial \(\eta^2 = 0.25\), main effect of group \(F_{(1,8)} = 0.44, p = .526\), group \(\times\) retrieval attempt interaction \(F_{(6,48)} = 0.43, p = .853\). As during learning, groups did not differ in their tendency to make perseverative win-stay errors to recently rewarded locations (Figure 3c,f; 1-s interval: \(t_8 = 1.26, p = .243\); 30-s interval: \(t_8 = 0.44, p = .674\)).

4 | DISCUSSION

In contrast to the finding with temporary inactivations (Forcelli et al., 2014), permanent hippocampal damage produced no decrement in accuracy in a nonnavigational spatial memory test. Contrary to the hypothesis that spared performance following permanent lesions might be achieved through a change in strategy, we found no difference in strategy between operated and control monkeys. This
confirms the first hypothesis proposed by Forcelli et al. (2014), that monkeys with permanent lesions would perform accurately, but does not support the second hypothesis, that those monkeys would learn the task via a different strategy. Because these two hypothesis work together to explain the discrepancy between the findings of Forcelli et al. (2014) with inactivation and other findings following permanent lesions, the present evidence bolsters the case that the hippocampus is not necessary for nonnavigational spatial tests that likely rely on egocentric memory (e.g., Lavenex & Lavenex, 2009).

The faster reaction times by hippocampectomized monkeys in this study are consistent with previous observations that hippocampal damage produces hyperactivity. Rats with hippocampal damage show hyperlocomotion (Sams-Dodd et al., 1997) and difficulty inhibiting premature responses (Abela et al., 2013), and monkeys with hippocampal damage show increased exploration and excitability (Machado & Bachevalier, 2006). In our monkeys, abnormally quick response times occur in several cognitive tests that include item memory, perception, and reward learning (unpublished data). Other labs have also noted anecdotally that monkeys with hippocampal damage are “hyper” (Elisabeth A. Murray, personal communication). Thus, the effect is not specific to tests of memory or spatial stimuli, and likely has broader implications for hippocampal function that are not specific to this task or to spatial memory. However, it does confirm that our lesions were substantial enough to affect behavior.

We found no support for the hypothesis that monkeys with permanent hippocampal lesions perform this test in a different way than control monkeys. First, although it has been suggested that hippocampal damage encourages reliance on a slower-learning habit-based system (e.g., Squire, 2004), we found no difference in time to learn the task. Second, we found no evidence that hippocampal damage encouraged any routinized pattern of responses to absolute spatial locations, such as always moving left to right. Instead, our monkeys behaved like those in the inactivation study, by starting directly in front of them and moving outward. Third, we found no evidence that hippocampal damage caused monkeys to prioritize choices to proximate or distal locations, such as might be encouraged by an egocentric nearest-neighbor travel path. Fourth, despite the possibility that hippocampal damage might produce an over-reliance on win-stay choices (McDonald & White, 1993), our monkeys with hippocampal damage did not make more win-stay errors to just-rewarded screen locations. It remains possible that the monkeys were using some alternative strategy that was not captured in learning rates, accuracy, spatial biases, choice distance, or perseverative errors. The most parsimonious explanation currently is that monkeys with hippocampal damage solve nonnavigational spatial tasks in the same way as do normal monkeys.

There are at least two ways to reconcile our findings with permanent lesions and those from the inactivation study. First, it is possible that the impairment following temporary hippocampal inactivation is an off-target effect involving areas outside the hippocampus. In a landmark study, Otchy et al. (2015) provided empirical evidence from representative species in two different phylogenetic classes, birds and rodents, that transient inactivations cannot be interpreted as if they are temporary lesions because they have additional short-term disruptive effects. For example, inactivation of NiF, an area in songbirds well-accepted as not critical for song production, robustly impairs song production due to its strong connections to area HVC, an area truly critical for song (Otchy et al., 2015). In contrast, after permanent lesions of NiF, both HVC activity and song production return to normal within hours. Thus, reliance solely on the inactivation data would give the false impression that the NiF was critical for song. One can think of this as a temporary ripple effect in an interconnected system, like an audience member fainting in the front row of a concert—they are not critical for the music, but the band will probably stop playing for a bit. The hippocampus is well-connected (Insausti et al., 2017). For example, the parahippocampal cortex (Alvarado & Bachevalier, 2005; Bachevalier & Nemanic, 2008; Malkova & Mishkin, 2003) and thalamus (Isseroff et al., 1982) have both been implicated in nonnavigational spatial memory, and both share strong connections with the hippocampal formation. In particular, some early claims of spatial memory deficits following aspiration lesions of the hippocampus were later found to be due to unintended damage of the parahippocampal cortex (Malkova & Mishkin, 2003), and even spatial memory deficits after excitotoxic lesions of the hippocampus correlate well with the amount of unintended parahippocampal damage (Blue et al., 2013).

Based on the empirical demonstrations that temporary inactivation causes temporary off-target spreading network disruption in two model species (Otchy et al., 2015), it is reasonable to posit that connected medial temporal lobe structures like the parahippocampal cortex are also temporarily disrupted during hippocampal inactivation. In contrast, there are several empirical demonstrations of normal function in connected temporal lobe structures after static hippocampal lesions (e.g., Bachevalier & Nemanic, 2008; Sakuda et al., 2006). Temporarily-disrupted function in a structure such as the parahippocampal cortex could explain why temporary but not permanent inactivation of the hippocampus impairs nonnavigational spatial memory tests, without invoking hippocampal function per se.

A second way the effects of inactivation and permanent lesions might be reconciled, is to consider the possibility that the physical Hamilton Search Task encourages an allocentric spatial coding that depends on the hippocampus, whereas the computerized analogue encourages an egocentric spatial coding that relies on nonhippocampal structures. This seems unlikely. If there were any such difference between the tasks, we should expect them to be in the opposite direction. In the inactivation study, boxes were arranged in a single horizontal row from the subject’s left to subject’s right, and the same positions for the boxes were used for every trial. In the present study we distributed the choice points across 24 possible screen locations, resulting in a variety of arrays across trials. A fixed horizontal array that repeated across trials should be more likely to encourage a routinized egocentric spatial code, whereas arrays that vary across both left–right and up–down axes might be expected to encourage a more allocentric encoding of each choice location with respect to the other locations in the array. But we cannot say this for certain without explicitly manipulating the layout of the choices. The mapping of navigational or nonnavigational spatial tests to the psychological constructs of allocentric or egocentric spatial memory is not straightforward. Because navigation typically involves moving through space in ways that change one’s relation to spatial landmarks, it is usually assumed to involve allocentric (world-oriented) spatial memory. In contrast, because nonnavigational tests usually maintain a fixed
relation of subject to landmarks, it is usually assumed to involve egocentric (self-oriented) spatial memory. Because both the screen and physical versions of the Hamilton Search Task involve a stationary subject, it is most parsimonious to assume both were readily solvable via egocentric spatial memory. The authors of the previous study conclude that it is impossible to know what spatial coding the monkeys used in their tasks without more direct tests (Forcelli et al., 2014). If the necessity of the primate hippocampus for nonnavigational tests of spatial memory does differ between small scale physical environments and screen-based locations, suggesting that one is more allocentric and another more egocentric, it will be an interesting challenge to determine why.

One potentially informative difference between our data and those of the inactivation study is that we found a robust accuracy difference between 30-s retention intervals and 1-s retention intervals (Figure 2), consistent with normal forgetting. In contrast, control accuracy in the inactivation study did not differ statistically as a function of retention interval duration (Forcelli et al., 2014). Interestingly, the number of correct choices in the first eight attempts during control sessions was actually numerically higher after the 30-s retention interval than the 1-s retention interval (Forcelli et al., 2014, Supporting Information Figures S1b and S3b), which is the opposite of how memory normally works. In the inactivation study, the 30-s interval was used specifically to make the use of working memory unlikely. One possibility is that the monkeys in the inactivation study were using a nonmnemonic strategy, such as postural mediation, to solve the task and that the hippocampal inactivation disrupted this nonmnemonic strategy. However, this possibility is speculative pending further experiments.

What is clear from the data presented here is that permanent, substantial, bilateral lesions of the primate hippocampus do not affect accuracy in this nonnavigational spatial memory task, which likely taps egocentric spatial memory. This remains in strong contrast to studies of navigational memory performance, which likely tap allocentric spatial memory processes, where memory is substantially impaired (Glavis-Bloom et al., 2013; Hampton, Hampstead, et al., 2004; Lavenex et al., 2006). Thus, the balance of evidence supports the critical role of the primate hippocampus in allocentric but not egocentric spatial memory.

ACKNOWLEDGMENTS
This project was supported in part by ORIP/OD P51OD011132, the National Science Foundation (Grants BCS-0745573: IOS-1146316, BCS-1632477), the National Institute of Mental Health (Grant R01MH082819), and the Intramural Research Program of the NIMH (ZIAMH002887). We thank Tara A. Dove-VanWormer, Emily Brown, Rachel Diamond, Victoria Templar, Thomas Hassett, Akshay Kohli, Celia Greenlaw, and Rebecca Cross for help running subjects. The authors declare no competing financial interests.

REFERENCES

ORCID
Benjamin M. Basile http://orcid.org/0000-0003-0642-0738