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# Hippocampal damage attenuates habituation to videos in monkeys

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## Abstract

Monkeys with selective damage to the hippocampus are often unimpaired in matching-to-sample tests but are reportedly impaired in visual paired comparison. While both tests assess recognition of previously seen images, delayed matching-to-sample may engage active memory maintenance whereas visual paired comparison may not. Passive memory tests that are not rewarded with food and that do not require extensive training may provide more sensitive measures of hippocampal function. To test this hypothesis, we assessed memory in monkeys with hippocampal damage and matched controls by providing them the opportunity to repeatedly view small sets of videos. Monkeys pressed a button to play each video. The same 10 videos were used for six consecutive days, after which 10 new videos were introduced in each of seven cycles of testing. Our measure of memory was the extent to which monkeys habituated with repeated presentations, watching fewer videos per session over time. Monkeys with hippocampal lesions habituated more slowly than did control monkeys, indicating poorer memory for previous viewings. Both groups dishabituated each time new videos were introduced. These results, like those from preferential viewing, suggest that the hippocampus may be especially important for memory of incidentally encoded events.

### Keywords

active encoding; hippocampal lesion; incidental encoding; memory; preferential viewing; primate

The hippocampus is known for its role in memory (Eichenbaum et al., 2016). In particular, spatial memory is reliably impaired by hippocampal damage across a wide range of species

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Author contributions

C.F-C., D.M. and J.R.Y. designed the experiments. C.F-C. performed the experiments and acquired the MS data. C.F-C. and S.M.B. analyzed the data. D.M., S.M.B., N.Y. and A.J.S. provided a critical input on the project. C.F-C. wrote the manuscript with input of all authors. J.R.Y conceived and supervised the project.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

including birds (Bingman & Yates, 1992; Hampton & Shettleworth, 1996), reptiles (Day, Crews, & Wilczynski, 2001), rodents (Duva et al., 1998; Moser, Moser, & Anderson, 1993; O'Keefe & Nadel, 1978), and monkeys (Glavis-Bloom, Alvarado, & Bachevalier, 2013; Hampton, Hampstead, & Murray, 2005; Lavenex, Amaral, & Lavenex, 2006). Reports of the effects of hippocampal damage on tests of item recognition are much more mixed (impairments: Alvarez, Zola-Morgan, & Squire, 1995; Mishkin, 1978; Zola et al., 2000; no impairments: Murray & Mishkin, 1998; Pascalis & Bachevalier, 1999). Thus, the role of the hippocampus in memory may be more constrained than currently recognized, at least in nonhumans.

Lack of selectivity of hippocampal damage has complicated the interpretation of several studies purported to assess hippocampal function. For example, monkeys with extensive damage to the medial temporal lobes were impaired in delayed nonmatching-to-sample at delays longer than 10 s and this impairment was attributed to the hippocampal damage (Alvarez et al., 1995; Mishkin, 1978; Zola et al., 2000), but later studies showed that these deficits could be fully accounted for by unintended damage to surrounding cortex (Gaffan & Murray, 1992; Suzuki, Zola-Morgan, Squire, & Amaral, 1993; Zola-morgan et al., 1989). Later studies did report that selective lesions of the hippocampus produced impairments in DNMS (Beason-held, Rosene, Killiany, & Moss, 1999; Squire, Kosslyn, Zola-Morgan, Haist, & Musen, 1992; Zola et al., 2000). Selective hippocampal lesions made neonatally that spared entorhinal and perirhinal cortex produced no recognition memory impairments in monkeys, even at delays longer than 10 min (Pascalis & Bachevalier, 1999). Large excitotoxic lesions of both hippocampus and amygdala, but not surrounding cortex, had no effect on nonmatching-to-sample (Murray & Mishkin, 1998). Lesions of the cortex surrounding the hippocampus produced severe impairments in object recognition in rodents and selective lesions to the hippocampus either produced mild impairments or no impairments at all (Mumby, Wood, & Pinel, 1992; Otto & Eichenbaum, 1992). Taken together, these results indicate little role in item recognition.

One possibility is that the hippocampus is primarily necessary for incidental encoding of memories, but that nonmatching-to-sample tests encourage active encoding (Nemanic, Alvarado, & Bachevalier, 2004). This idea has received support from studies of human patients showing that visual paired comparison performance is more sensitive to hippocampal damage than is nonmatching-to-sample performance (Pascalis, Hunkin, Holdstock, Isaac, & Mayes, 2004). Most implementations of nonmatching-to-sample involve short delays and extensive training, which may encourage active encoding strategies that rely on working memory and brain areas other than the hippocampus (Fuster, Bauer, & Jervey, 1985; Miller, Erickson, & Desimone, 1996).

Consistent with a role in incidental encoding, deficits in memory following hippocampal damage are more consistently found with the visual paired comparison task in both humans and monkeys. Monkeys with hippocampal lesions performed normally on nonmatching-to-sample while showing a delay dependent deficit in visual paired comparison (Nemanic et al., 2004; Pascalis & Bachevalier, 1999). Similarly, human amnesic patients with selective hippocampal damage show the same dissociation (Munoz, Chadwick, Perez-Hernandez, VargahKhadem, & Mishkin, 2011). This task is considered an incidental encoding task

because subjects are not required to actively memorize presented stimuli. Memory is inferred by longer looking times to novel stimuli compared to simultaneously presented familiar stimuli.

To test for converging evidence that the hippocampus is critical for incidental memory, we evaluated monkeys with selective hippocampal lesions in a novel memory paradigm with no food reward and no explicit memory requirement. Monkeys viewed short videos that repeated within and across days and we operationalized memory as decreased interest in watching the same videos over time. The monkeys saw a single set of 10 videos daily for a week. Monkeys started each video by pressing a button, allowing us to track how many times they watched the videos. There was no explicit contingency to promote active memory. If the hippocampus supports incidental encoding of the videos, then monkeys with hippocampal lesions should show blunted habituation.

We tested nine adult male rhesus monkeys in their home cages using portable testing rigs consisting of a 15-in. color liquid crystal display touch-sensitive screen (Elo TouchSystems, Menlo Park, CA) operating with a resolution of 1,024 × 768 pixels. Testing was controlled by a personal computer with a custom program written in Visual Studio 2013 (Microsoft Corporation). Monkeys were tested 6 days a week, Sunday through Friday, for 30 min each day, starting at 10 a.m. Monkeys touched a centrally presented red dot twice to initiate each video clip (1,024 × 768 pixels). The dot reappeared after each video, allowing the monkeys to initiate the next video in the sequence of 10 videos in use that week. The same sequence of 10 videos was available for 30 min each day, and for six consecutive days, Sunday through Friday (Figure 1). On the following Sunday, a new set of 10 videos was introduced. This entire process was repeated seven times, for a total of 70 videos. Videos were collected from youtube. com using a free YouTube video downloader extension obtained from the chrome internet browser, were edited to 7 s each, and were presented without sound. Content of videos was not restricted to any category and ranged from clips of animal behavior to clips from classic movies. The order in which videos were used was determined by randomly shuffling the set of 70 videos once at the start of the study. All monkeys experienced videos in the same order.

Four of the monkeys tested had bilateral excitotoxic lesions of the hippocampus, and five were unoperated controls. The surgical procedure used has been previously described (Hampton, Buckmaster, Anuszkiewicz-Lundgren, & Murray, 2004). Lesions included the majority of the hippocampus bilaterally, resulting in an average 55.6% volume reduction, for an average of 70.3% estimated damage using the regression equation of Malkova et al. (2001; Figure 2; Table 1, for full description of procedure and damage assessment see Basile & Hampton, 2019). Whenever possible, monkeys were pair-housed when not testing. Pair-housed monkeys were separated during testing by a protected-contact divider that allowed 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 touch screen-based cognitive tasks. All procedures complied with U.S. law and the National Research Council guide for the care and use of laboratory animals.

Because the number of videos watched decreased across days, the distribution of our count data was significantly positively skewed (Shapiro–Wilk test: $p = .003$). Mean counts were log transformed to approximate normality (Shapiro–Wilk test: $p = .111$). The log transformed data were then submitted to an analysis of variance with lesion group as a between subjects factor and day as a repeated measures factor, for which assumptions of sphericity were not violated.

Monkeys with lesions of the hippocampus showed significantly reduced habituation compared to intact monkeys (Figure 3; Day × Group interaction: $F_{(5,35)} = 4.37$, $p = .003$, $\eta^2 = .384$). The groups did not differ significantly in the number of videos watched on Day 1 of each week, indicating that the blunted habituation was not a result of an overall higher rate of watching videos in the lesion group (control: $M = 96.7$, lesion: $M = 103.3$, $t_{(7)} = .472$, $p = .651$). Across each week, both groups of monkeys showed evidence of habituation (main effect of day: $F_{(5,35)} = 53.6$, $p < .001$, $\eta^2 = .884$; main effect of group: $F_{(1,7)} = 1.77$, $p = .225$, $\eta^2 = .202$) indicating that although the monkeys with lesions showed a blunted rate of habituation, they still showed some evidence of memory.

The difference in habituation to videos observed here should be interpreted as a memory effect, rather than a difference in interest in videos. This is indicated by the fact that monkeys did not differ in the number of videos watched on Day 1 across the seven cycles of the experiment (see Figure 4 for a week by week representation of these results). This suggests that it was the specific content of the videos that controlled behavior for both groups. Number of videos viewed was not limited by a ceiling effect. If the monkeys were to touch the red button immediately after each video through 30 min, they could watch up to 257 videos, but none came close to this maximum (mean for Day 1 = 96.7 and 103.3 for control and lesion groups, respectively; maximum was 152). Hippocampal removal has been known to produce hyperactive behavior in monkeys (Machado & Bachevalier, 2006) and rats (Sams-Dodd, Lipska, & Weinberger, 1997). Thus a possibility is that our hippocampal monkeys watched more videos due to disinhibition. However, there was no difference in number of watches on Day 1 with each video set between groups, and the number of watches was well below the ceiling set by the time available for watching videos each day. Hyperactivity is unlikely to account for the difference between groups. Because we did not make video recordings of the behavior of monkeys, we cannot be certain that they always viewed the videos. However, the habituation with repeated exposures and the dishabituation at the beginning of each week suggests they did attend. Nonetheless, it is possible that the hippocampal group attended less, producing the difference we observed between the groups.

Our findings converge with previous findings in monkeys (Jutras & Buffalo, 2010; Nemanic et al., 2004; Pascalis & Bachevalier, 1999; Zola et al., 2000) and human amnesic patients (Manns et al., 2003; Mckee & Squire, 1993; Munoz et al., 2011; Pascalis et al., 2004; Smith, Hopkins, & Squire, 2006) suggesting that visual paired comparison measures hippocampal-dependent memory. This contrasts with negative results found in monkeys tested with nonmatching-to-sample (Murray & Mishkin, 1998; Nemanic et al., 2004; Pascalis & Bachevalier, 1999; Suzuki et al., 1993; Zola-morgan et al., 1989). A critical difference between these tests of memory is that nonmatching-to-sample promotes active encoding, whereas visual paired comparison does not. Thus, in visual paired comparison, participants

are thought to engage in incidental encoding, or encoding without any explicit strategy to remember in the future (Manns, Stark, & Squire, 2000; Munoz et al., 2011). Nonmatching-to-sample variants involve extensive training, require a specific response, and deliver food or juice reward. In contrast visual paired comparison and video habituation have none of these features. The incidental/active encoding distinction remains the most likely explanation for why the hippocampus is critical for some of these tasks and not others, but future work should assess the relevance of all factors that differ between these tasks.

This paradigm may prove useful as another method to assess hippocampal function in monkeys and humans. Future studies should determine the extent to which deficits in incidental memory result from loss of the very same memory process responsible for explicit memory deficits in amnesia, or are instead a signature of a distinct function in a constellation of functions dependent on the hippocampus.

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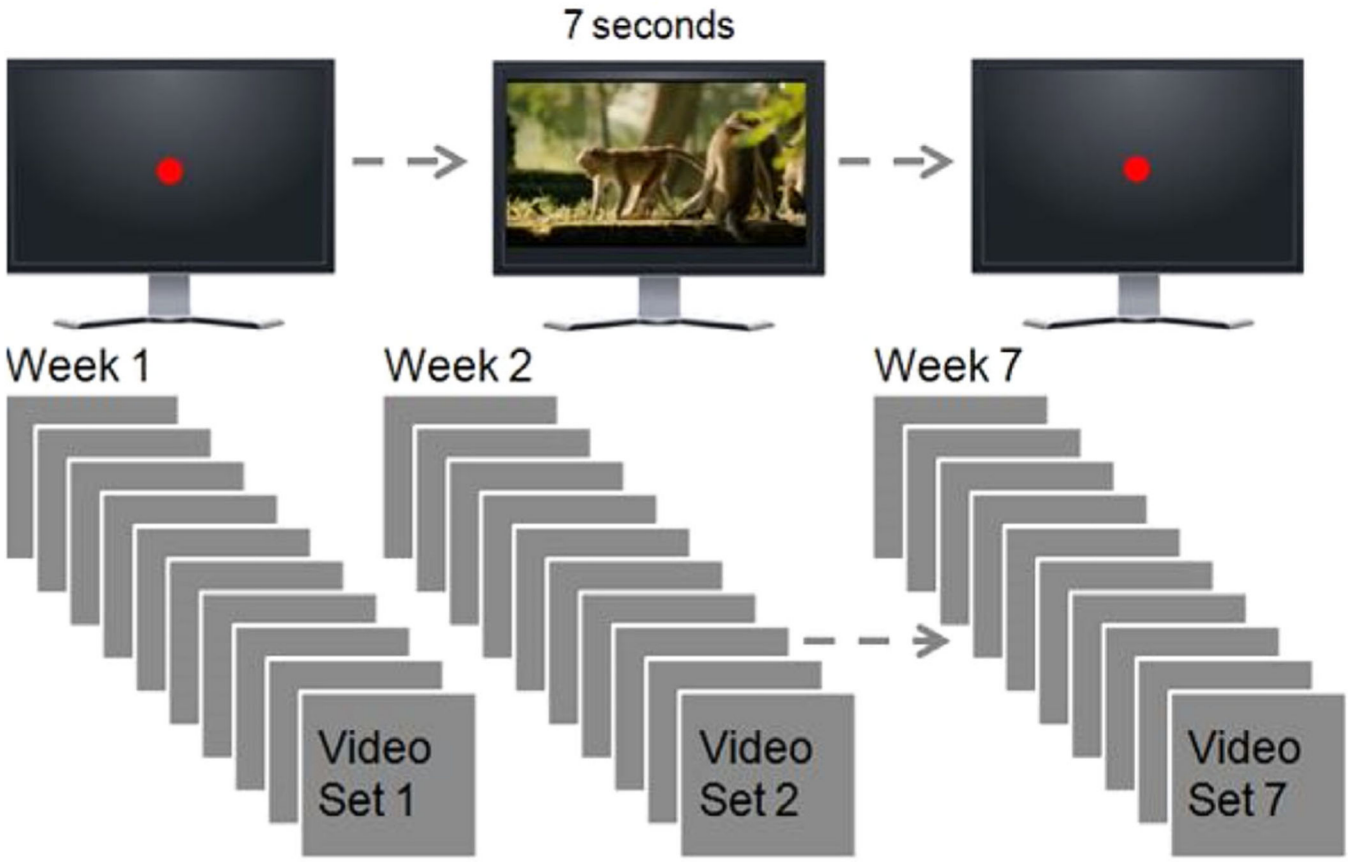


**FIGURE 1.**

Video habituation paradigm. Monkeys tapped a red dot to start one of ten 7-s videos. Once the first video ended, touching the dot started the next video in the sequence of 10. After the tenth video, the cycle started back at Video 1. Monkeys were allowed 30 min to watch videos each day. Each week, a new set of 10 videos was introduced

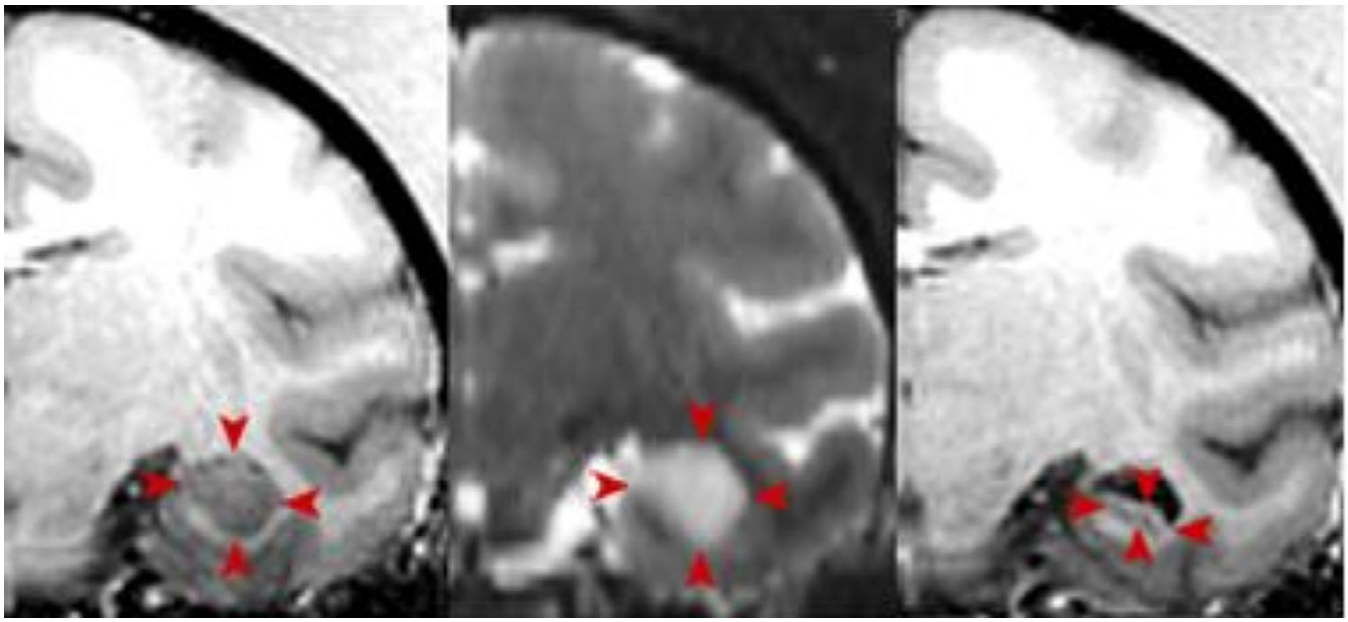

**FIGURE 2.**

Hippocampus damage assessment from Basile and Hampton (2019). Coronal view of one hemisphere indicating areas measured. Left: Presurgery T1 scan used for targeting. Middle: Postsurgery T2 scan used to verify successful injection. The white hypersignal in the hippocampus reflects edema that predicts subsequent damage. Right: The shrunken hippocampus in a final T1 scan used to quantify damage. The enlarged ventricle is evident as the large black area superior to the shrunken hippocampus. Red arrows indicate the boundaries of the hippocampus

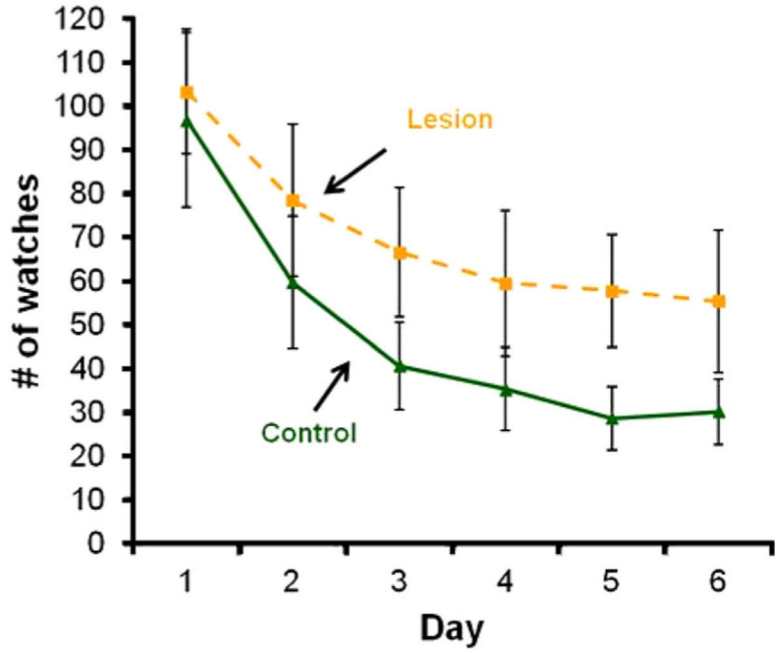


**FIGURE 3.**

Monkeys with hippocampal lesions showed blunted habituation to videos. Both lesion and control monkeys start Day 1 of each week watching a similar number of videos. Both groups also habituate to each video set by the end of the week. However, the rate of habituation is significantly blunted in monkeys with hippocampal lesions, indicating a memory deficit. Error bars for each data point represent standard error of the mean

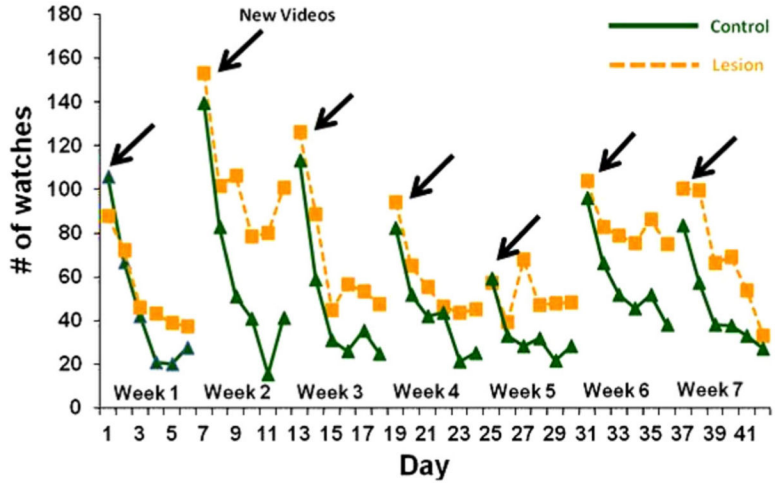


**FIGURE 4.**

Number of videos watched each day across the seven cycles of the experiment. In each of 7 weeks of testing, monkeys showed initially high interest in new videos, but habituated with repeated exposures. This suggests that the specific content of the videos controlled behavior and that habituation indicates memory for specific videos

**TABLE 1**

MRI estimated hippocampal damage (from Basile & Hampton, 2019)

| | | % volume reduction[a] | | | % estimated damage[b] | | |
|---|---|---|---|---|---|---|---|
| **Monkey** | **Surgeries** | **Left** | **Right** | **Total[c]** | **Left** | **Right** | **Total[c]** |
| Ap | 2 | 61.2 | 59.1 | 60.2 | 77.6 | 74.9 | 76.3 |
| Be | 1 | 42.8 | 59.0 | 50.7 | 53.4 | 74.8 | 63.7 |
| Ne | 1 | 60.8 | 56.2 | 58.6 | 77.1 | 71.1 | 74.2 |
| Es | 2 | 43.0 | 49.0 | 46.0 | 53.6 | 61.5 | 57.5 |
| Mi | 2 | 60.5 | 65.2 | 62.8 | 76.7 | 83.0 | 79.8 |
| Median | | 60.5 | 59.0 | 58.6 | 76.7 | 74.8 | 74.2 |
| Mean | | 53.6 | 57.7 | 55.6 | 67.7 | 73.1 | 70.3 |

[a](1 − [postoperative volume/preoperative volume]) × 100.

[b]Calculated based on Malkova et al. (2001) and Hampton et al. (2004).

[c]Calculated from total hippocampal volume (i.e., left volume + right volume).