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LETTER TO THE EDITORS

The Role of the Hippocampus in Declarative Memory: A Reply to Nadel

Stuart Zola-Morgan,[1] Larry R. Squire,[1,2] and Seth J. Ramus[2]

[1]Veterans Affairs Medical Center, San Diego, and Departments of Psychiatry and [2]Neurosciences, U.C.S.D. School of Medicine, La Jolla, California

In Nadel's comment on our study (Zola-Morgan et al., 1994), he reiterates the view that the hippocampus has a selective role in spatial memory, i.e., the hippocampus stores information about nonegocentric space (viewpoint-independent space; O'Keefe and Nadel, 1978; Nadel, 1991). In the context of our report, he points out that four monkeys with lesions limited to the hippocampal region (the H lesion, which includes the cell fields of the hippocampus proper, the dentate gyrus, and the subiculum) were impaired on the delayed nonmatching to sample task only at a delay of 10 min[1], and not at shorter delays of 15 s and 60 s. The monkeys were removed from the testing apparatus during the 10-min delay and returned to their home cages. Because task performance under this condition could conceivably require re-identifying the spatial context in which the sample was originally presented, Nadel suggests that this version of the nonmatching task, with long delays, could be construed as a spatial memory task and that our results could therefore be interpreted as supporting the spatial mapping theory of hippocampal function.

To our mind, Nadel's commentary simply identifies that our study (which was designed to determine the severity of impairment following H lesions and other lesions, not to distinguish between theories of hippocampal function) may be consistent with more than one view of hippocampal function. In the sections that follow, we make two specific points about our findings, one about removing animals from the testing apparatus and one about the nature of the lesions. We then make a more general point about the spatial memory hypothesis of hippocampal function.

[1]The four monkeys in the H group were also impaired at a delay interval of 40 min (Alvarez et al., 1995). The data from the 40-min delay interval were not included in Zola-Morgan et al. (1994), because the H group was the only group tested at a 40-min delay.

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Address correspondence and reprint requests to Stuart Zola-Morgan, Department of Psychiatry 0603, U.C.S.D. School of Medicine, La Jolla, CA 92093.

REMOVING ANIMALS FROM THE TESTING APPARATUS

It is unclear to us why removing monkeys from the testing apparatus during a delay interval necessarily introduces an important spatial component into the task. Could not a monkey make a novel-familiar discrimination between two objects even if the monkey were "lost" with respect to its environment? In addition, although it is true that monkeys with H lesions were impaired when they were removed from the apparatus during the delay interval, this manipulation was confounded with the length of the delay interval. Specifically, monkeys with H lesions were impaired at the long delay but not at short delays. Accordingly, within the context of this single study, one cannot decide whether the important factor was the length of the delay or the fact that the animals were removed from the apparatus.

Other findings favor the idea that the length of the delay interval itself is important in determining the effects of lesions limited to the hippocampal region. For example, monkeys with ischemic lesions limited to the hippocampal region exhibit statistically significant deficits even at relatively short delays when they remain in the apparatus during the delay interval (see Zola-Morgan et al., 1994; Table 1, 15 s: N group = 94% correct, ISC group = 85% correct, $P < .05$). Moreover, as we reported more recently (Alvarez et al., 1995), monkeys with H lesions were impaired at very short delays (8 s) during the first ten trials of the 1st day of training on the nonmatching task. At this early stage of training, animals presumably have not learned the rule that determines the availability of reward, and performance on the choice phase of the trial likely reflects a spontaneous preference to select the novel object that was not presented as the sample. Normal monkeys exhibited a strong tendency for novelty. Monkeys with H lesions did not. Elsewhere (Alvarez et al., 1994), we have interpreted the findings at short and long delays following hippocampal damage in monkeys as evidence that hippocampal damage causes an impairment in declarative memory.

We have also evaluated directly the implication of Nadel's suggestion that, unlike the shorter delay intervals, the 10-min delay interval creates a special problem for the animal, i.e., after returning to the testing apparatus from the home cage, the monkey must recognize the spatial context and select the appropriate object stimulus in that context (Nadel, p. 5). One implication of this suggestion is that monkeys might treat the 10-min

TABLE 1.

Factor Analysis for the Measures From the Test Battery[1]

Variable	Factor 1	Factor 2
A. Six measures (from Zola-Morgan et al., 1994)		
DNMTS1-TRIALS	−.775	−.107
DNMTS1-DELAYS	.823	.255
DNMTS2-DELAYS	.827	−.136
Object	.784	−.374
Pattern	.151	.787
Concurrent	−.164	.855
B. Six measures (10-min delay interval removed)		
DNMTS1-TRIALS	−.775	−.065
DNMTS1-DShort	.792	.333
DNMTS2-DShort	.793	−.124
Object	.823	−.319
Pattern	.167	.815
Concurrent	−.226	.843
C. Eight measures (10-min delay separate from shorter delays)		
DNMTS1-TRIALS	−.766	−.045
DNMTS1-DShort	.775	.305
DNMTS2-DShort	.716	−.182
DNMTS1-D10min	.559	.133
DNMTS2-D10min	.787	−0.76
Object	.807	−.348
Pattern	.165	.809
Concurrent	−.183	.838

[1]The factor-loadings in the two columns were based on principal-components extraction with varimax rotation of the scores of all 42 monkeys (Zola-Morgan et al., 1994). The boxes outline the measures from the test battery that loaded strongly on each factor. **A:** Table originally presented in Zola-Morgan et al. (1994). **B:** Principal-components extraction of the data in A without the data from the 10-min delay interval. **C:** Principal-components extraction of the data in A with the data from the 10-min delay interval and the data from the shorter delays considered separately. **Abbreviations:** DNMTS1-TRIALS, the N. of trials required to obtain learning criterion on the trial-unique delayed nonmatching to sample task the first time it was administered; DNMTS1-DELAYS, the percent correct score averaged across the 15-s, 60-s, and 10-min delay intervals from first administration of the trial-unique delayed nonmatching to sample task; Pattern, the average N. of trials required to obtain learning criterion on the two pattern discrimination tasks; Object, the percent correct score averaged across all 3 test days for all four object pairs of the delayed retention of object discriminations task; Concurrent, the N. of trials required to obtain learning criterion on the concurrent discrimination task; DNMTS2-DELAYS, the percent correct score averaged across the 15-s, 60-s, and 10-min delay intervals from the second administration of the trial-unique delayed nonmatching to sample task; DNMTS1-DShort, the percent correct score averaged across the 15-s and 60-s delay intervals from the first administration of the trial-unique delayed nonmatching to sample task; DNMTS2-DShort, the percent correct score averaged across the 15-s and 60-s delay intervals from the second administration of the trial-unique delayed nonmatching to sample task; DNMTS1-D10min, the percent correct score on the 10-min delay interval from the first administration of the trial-unique delayed nonmatching to sample task; DN-

delay interval in a fundamentally different way than the shorter delay intervals. In the factor analysis procedures reported in our study (Zola-Morgan et al., 1994), data from the 15-s, 60-s, and 10-min delays were averaged together to constitute a single variable.[2] Using the same 42 monkeys reported in Zola-Morgan et al. (1994), we have repeated the factor analysis under two different conditions (see Zola-Morgan et al., 1994, for a description of the variables used in the original analysis). In the first condition, we eliminated the 10-min delay data from the analysis. In the second condition, we treated the data from the 10-min delay and the data from the shorter delays (15 s and 60 s) as separate variables (Table 1). For each condition, principle-components extractions with varimax rotations of the data revealed similar patterns of factor loadings. In addition, the patterns were similar to what we found in the original analysis, in that the same measures loaded onto the same factors. Importantly, when the 10-min delay variable was considered separately, it loaded onto the same factor as the shorter delay variables. Thus, we could find no evidence that the 10-min delay interval of the delayed nonmatching to sample task is fundamentally different from the shorter delays or from the other measures of what we have termed declarative memory.

THE NATURE OF THE LESION

It is unclear to us what lesion is the relevant one for addressing the spatial memory hypothesis. This point is not trivial because lesions that have been used to study the effects of "hippocampal" function have varied in their locus and extent. Lesions have been directed variously at the fornix, the hippocampus proper, the hippocampus plus subiculum, and the entire hippocampal formation (hippocampus, dentate gyrus, subicular complex, and entorhinal cortex). Moreover, different techniques have been used to produce these lesions including aspiration, electrolytic and radiofrequency methods that do not spare fibers of passage, and neurotoxins such as ibotenic acid that do largely spare fibers of passage. Other neurotoxins have also been used, including separate and combined applications of kainic acid and colchicine. Like ibotenic acid, these neurotoxins largely spare fibers of passage, but they can cause more damage than ibotenic acid to structures outside the hippocampus (e.g., subiculum and entorhinal cortex; Jarrard and Meldrum, 1993).

An additional difficulty is a long-standing imprecision with respect to hippocampal terminology. Specifically, different terms are sometimes used interchangeably, e.g., hippocampus (which includes the hippocampal cell fields and the dentate gyrus), the hippocampal region (which includes the hippocampus and the subicular complex), and the hippocampal formation (which includes the hippocampal region and the entorhinal cortex). In this sense, Nadel could have regarded our study, which involved monkeys with subicular and dentate gyrus damage in addition to damage of the hippocampus proper, as irrelevant to the spatial mapping view, holding that only lesions limited to the hippocampus proper should provide a fair test of the idea.

These points about our own study notwithstanding, it seems to us that a debate of spatial and nonspatial theories of hippocampal function in the context of our study is entirely misplaced. It is more useful to remind ourselves that many other experimental findings have been reported during the past 20 years that have been offered as evidence against a strictly spatial account of hippocampal function. These have already been reviewed in some detail previously (Squire, 1979; 1992), and as part of a *Hippocampus* Forum (1991, 1:221–292) that included ten essays explicitly critical of the idea that the hippocampus is exclusively involved in spatial function.

The point is that the literature provides ample evidence that lesions that disrupt hippocampal function impair nonspatial memory as well as spatial memory. Moreover, there is no evidence that spatial memory impairment is disproportionately severe in comparison to nonspatial memory impairment, and there is some evidence that impairments in these two domains are proportional (Cave and Squire, 1991). The following paragraphs first identify some of the lesion studies in which disruption of hippocampal function impaired performance on *nonspatial* memory tasks (we have not included our own findings from monkeys here), and then neurophysiological studies in which the activity of hippocampal cells in behaving animals correlated with *nonspatial* features of tasks.

LESION STUDIES

In rats, disruption of hippocampal function by radiofrequency lesions of the fornix caused severe impairment in olfactory dis-

[2]Nadel suggests that when one pools data across tasks, as we did in our z-score analysis, one might tap into quite distinct learning abilities and different underlying neural substrates. In this way, one creates the possibility of a misleading conclusion because the procedure of pooling presupposes that the tasks are measuring the same sort of thing. We do not disagree with Nadel's cautionary note. However, what Nadel cautions us about, i.e., ". . . lump[ing] together results from tasks tapping . . . varied forms of memory" (p. 6), is not what we did, and we are puzzled by his comments on this point. Specifically, as described in our article, before carrying out the z-score analysis, we first submitted the data from 42 monkeys for each of five tasks (trial unique delayed nonmatching to sample, pattern discrimination, delayed retention of object discriminations, concurrent discrimination learning, and delayed nonmatching to sample retest) to a correlational analysis and a factor analysis. With these analyses we sought to identify tasks that were strongly intercorrelated and sensitive to medial temporal lobe damage and other tasks that were intercorrelated but less sensitive or insensitive to medial temporal lobe damage. Only the data from three tasks (delayed nonmatching to sample, delayed retention of object discriminations, and delayed nonmatching to sample retest) that proved sensitive to medial temporal lobe damage were then carried forward and used in the z-score analysis. These tasks were strongly and significantly intercorrelated (all $Ps < .01$), and they loaded strongly on the first of two factors. It seems to us that a reasonable interpretation of the results of these procedures is that the findings reflect the dependence of all three tasks on the integrity of the medial temporal lobe.

crimination learning when odors were presented simultaneously (Eichenbaum et al., 1988, 1989), severe impairment on a nonspatial delayed matching to sample task (Raffaele and Olton, 1988), and severe impairment on an enclosed radial arm maze in which each arm contained a distinctive set of discriminative stimuli such that spatial cues could not be used to solve the problem (Olton and Feustle, 1981). Rats with electrolytic lesions of the hippocampal region (including the hippocampus proper, the dentate gyrus, and the subiculum) were also impaired in retaining a postoperatively acquired food preference when a long delay interval (greater than 24 h) was used (Winocur, 1990). Finally, rats with ibotenic acid lesions of the hippocampus were impaired in learning that the level of food deprivation signaled shock, but were unimpaired in the same paradigm when cued by auditory stimuli (Davidson and Jarrard, 1993).

In rabbits, aspiration lesions of the hippocampal region impaired reversal performance in two-tone discrimination reversal conditioning of the rabbit nictitating membrane response (Berger and Orr, 1983). Lesions of the hippocampal region in rabbits also disrupted acquisition of long-latency conditioned responses of the nictitating membrane in trace conditioning paradigms (Solomon et al., 1986; Kim, et al., 1995).

In rats, lesions of the hippocampal formation (including the hippocampal region and the entorhinal cortex) made by colchicine and kainic acid injections impaired performance on the transverse-patterning problem, a visual discrimination task whose solution requires an animal to form configural associations to compound stimuli (Alvarado and Rudy, in press). Hippocampal lesions made by ibotenic acid were also reported to impair performance on the transverse-patterning problem as well as on the negative-patterning problem (Rudy and Sutherland, 1989; Alvarado and Rudy, 1993), another of the class of problems thought to be solvable only if the subject can acquire configural associations.

NEUROPHYSIOLOGICAL STUDIES

In a modified radial arm maze, approximately 19% of hippocampal complex spike cells in rats exhibited activity in association with cue type and not with spatial location. Moreover, many hippocampal cells (42%) responded to a combination of spatial and nonspatial cues, "indicating that most hippocampal neurons encoded conjunctions or relations between spatial and local cue information" (Young et al., 1994). Studies of recognition memory in rats found that in an odor-guided continuous delayed nonmatching to sample task (Otto and Eichenbaum, 1992), neurons in the CA1 field fired differentially to the "match" and "nonmatch" relationship between stimuli. That is, cellular activity reflected the results of comparisons between the sample and match cues. In another study of successive odor discrimination, increased firing rates of hippocampal neurons during odor sampling was found to be contingent on the odor presented in the previous trial (Eichenbaum et al., 1987).

In rabbits, hippocampal pyramidal cells exhibited learning-related plasticity that developed gradually over the course of classical conditioning of the nictitating membrane response (Solomon et al., 1986). In monkeys, cells in the anterior hippocampal region were responsive to the delay intervals in auditory-visual and visual-visual delayed matching to sample tasks. As the delay period progressed, some cells in the hippocampal region (excitatory delay neurons) increased their activity during the delay interval compared to activity during the intertrial interval (Colombo and Gross, 1994). Moreover, there was a higher probability of encountering a delay neuron when the monkey was performing between 75% and 100% correct than when the monkey was performing between 50% and 75% correct. It is difficult to understand these changes in hippocampal unit activity in terms of any spatial factor.

FINDINGS FROM HUMAN AMNESIA

It is also worth emphasizing that the findings from experimental animals are in agreement with the findings from amnesic patients. Four well-studied amnesic patients have now been described with damage to the hippocampal region. In two cases, the damage was restricted primarily to the CA1 pyramidal cell field of the hippocampus (Zola-Morgan et al., 1986; patient G.D. in Rempel-Clower et al., 1994). In two other cases, the damage involved all the CA fields of the hippocampus and the dentate gyrus (Victor and Agamanolis, 1990; patient LM in Rempel-Clower et al., 1994; in patient LM, slight cell loss was also detectable in the entorhinal cortex, presumably from retrograde degeneration associated with damage to the dentate gyrus). There is no hint that these patients can be characterized as having a special problem with spatial memory. Patients with amnesia do have impaired spatial memory, but they also forget prose passages, tactual impressions, odors, faces, and melodies (Squire, 1992).

The possibility that hippocampal lesions might impair spatial memory disproportionally more than nonspatial memory deficits was tested directly in amnesic patients (Cave and Squire, 1991). Fourteen amnesic patients, including those with confirmed damage to the hippocampal region, first inspected an array of toy objects. After a retention interval, they were given two nonspatial memory tasks, i.e., they were asked to recall the names of the objects, and to recognize the names of the objects on a multiple-choice test. They were also given a spatial memory task, i.e., they were asked to place the objects in their original position in the array. When performance of the amnesic patients on the two object-memory tests was matched to the object-memory performance of the control subjects (by testing the control subjects after a long retention interval), spatial memory performance was equivalent for amnesic patients and control subjects. Thus, the impairment in spatial memory was proportional to the impairment in object recall and object recognition.

We can find no evidence that the mammalian hippocampus is disproportionally involved in spatial memory. Lesion studies involving a wide range of tasks and stimulus modalities suggest that the hippocampus is important in spatial memory but that it

plays no special role in this regard. Moreover, neurophysiological studies of hippocampal function make this same point. Spatial memory appears to be just one example of a broad array of memory abilities dependent on the hippocampal region.

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