LETTER TO THE EDITORS

The Role of the Hippocampus in Declarative Memory: A Comment on Zola-Morgan, Squire, and Ramus (1994)

Lynn Nadel

Department of Psychology and ARL Neural Systems, Memory and Aging Division, University of Arizona, Tucson, Arizona

In a recent article (Zola-Morgan et al., 1994), a set of data were presented in support of the view that "damage limited to the hippocampus proper, the dentate gyrus, and the subicular complex causes significant memory impairment" (p. 493). These data come from a series of elegant studies utilizing monkeys tested on a standard battery of tasks, several of which are taken as requiring the involvement of a proposed declarative memory system, a hypothetical construct composed in humans of memory for facts and events that can be called up to conscious recollection. This claim, and these data, are critical in evaluating the current debate between proponents of cognitive/spatial map theory (e.g., O'Keefe and Conway, 1978; Nadel, 1991; O'Keefe, 1991) and those of declarative theory (e.g., Squire, 1992; Cohen and Eichenbaum, 1993). For that reason, the present note seeks to clarify exactly what can, and cannot, be concluded from the reported results.

To begin, it is important to clarify the distinction between cognitive map theory and declarative memory theory. Both theories have addressed the selective role that the hippocampus plays in memory. Both theories agree that there are many forms of memory that do not require the functioning of the hippocampus. The cognitive map theory asserts that the hippocampus is essential only for the kind of memory that incorporates spatial information, which includes memory for places, environments, or spatial contexts and episodes, and for the exploratory behavior during which animals incorporate novel information into their cognitive maps. Declarative theory is silent about exploration of novelty, and asserts that the stated categories of spatial memory are merely very good examples of the broader category of memories involving facts and events. The two theories diverge on the issue of the role of hippocampus in exploration, and in just those memories that have nothing to do with space, contexts, or episodes. Hence, data from studies using tasks that are demonstrably non-spatial have been taken as a critical testing ground for contrasting these two theories. There is no debate about the role of the hippocampus in learning about places and contexts, which is well established in the literature in all species so far examined.

Zola-Morgan et al. (1994) are concerned with the impact of a variety of lesions in the medial temporal lobe, including monkeys with lesions limited to the hippocampus proper, dentate gyrus, and subiculum (H group), and those with lesions going beyond the hippocampus proper, dentate gyrus, and subiculum to include the adjacent entorhinal cortex and parahippocampal gyrus (the H+ group) and the perirhinal cortex and anterior entorhinal cortex (the H++ group). In this note I will not address the broader claims the authors make about the role of structures beyond those involved in the H group, nor will I address the proposed nature of declarative memory; I have addressed some of these points elsewhere (Nadel, 1991, 1992, 1994).

This commentary is focused on the data from the eight monkeys in the H group, and what can be concluded from these data about the functions of the hippocampus. Of these animals, four received radiofrequency lesions (H-RF) and four received ischemic lesions (H-ISC). The authors analyzed performance of the lesioned animals on a battery of five tasks, given to all the animals in sequence: trial-unique delayed nonmatching to sample (DNMTS-1), pattern discrimination, delayed retention of object discriminations (OBJECT), concurrent discrimination learning, and a retest of trial-unique delayed nonmatching to sample (DNMTS-2). Based on correlational analyses and a factor analysis of these data, it was concluded that only the DNMTS task and delayed retention of object discrimination unambiguously tapped declarative memory. Data from these two tasks were then used in an analysis of the extent to which damage in various parts of the medial temporal lobe caused deficits in declarative memory. In order to do this a single z score was computed for each monkey, using the data from both DNMTS-1 and DNMTS-2 and the OBJECT task. The data from DNMTS were treated in the following way: one measure was derived from the number of trials to reach criterion (90/100) on DNMTS-1, during which an 8-s retention interval was used. Another measure was derived from the percent correct scores obtained during 100 post-criterion trials given with 15-s retention interval, 100 such trials given with 60-s retention interval, and 50 such trials given with 10-min retention interval. The animals received 20 trials/day in the 15-s and 60-s conditions, followed by five trials/day in the 10-min condition. Critically, a single percent correct score was obtained by averaging across the three retention intervals in each case. A separate score was derived for DNMTS-1 and for DNMTS-2.

Thus, the z score for each animal was generated from four data points: a percent correct score for OBJECT discrimination retention, a score on trials to criterion on initial learning of the DNMTS, and two scores generated by averaging across percent correct for all three delay retention intervals used (15 s, 60 s, 10 min) in DNM- TBS-1 and DNMTS-2.

Combining all these data into a single Z score, it appears that H lesions cause a statistically significant, but
The data on the four H-ISC animals in the H group appear in worse than controls in most cases, this reaches significance only in group. In Alvarez et al. (1995) the data for the four H-RF animals with the OBJECT discrimination retention task. In Zola-Morgan consider each task, and each retention interval, in its own right. animals in the H group, who received radiofrequency lesions of the hippocampus, dentate gyrus, and subiculum, have been referred to in several publications (e.g., Clower et al., 1991; Squire, 1994), and are about to be published (Alvarez et al., 1995).

Let us consider each task and condition separately, beginning with the OBJECT discrimination retention task. In Zola-Morgan et al. (1992), the data on the OBJECT task for the four H-ISC animals are presented in Table 2. The percent correct scores averaged across 3 test days (the same measure used in Zola-Morgan et al. 1994) were 86% for the control group (N) and 85% for the H-ISC group. In Alvarez et al. (1995) the data for the four H-RF animals are presented in Table 1. The percent correct score averaged across three test days for these animals was 85%. Thus, the data from the OBJECT task are absolutely clear: there is no deficit whatever in the retention of object discrimination in monkeys with lesions restricted to the hippocampus proper, dentate gyrus and subiculum.1,2

Consider next the data from the DNMTS task, taking into account the different retention intervals used. Once again the raw data are presented in Zola-Morgan et al. (1992), in Table 1 and Figure 10, and in Alvarez et al. (1995) in Table 1 and Figures 3 and 4. What these data seem to show is that in both the H-ISC and H-RF animals a deficit is generally observed only at the 10-min retention interval; although the H animals are numerically worse than controls in most cases, this reaches significance only in the H-ISC animals at 15 s (in DNMTS-1), and in the H-ISC and H-RF animals at 10 min. It is also clear from Alvarez et al. (1995) that the performance averaged across all three retention intervals (using data from DNMTS-1 and DNMTS-2 together) did not differ between H-RF and control monkeys (85% and 87%, respectively). By contrast, Zola-Morgan et al. (1992) state that on this measure (performance averaged across the three intervals) the H-ISC monkeys were impaired relative to the N monkeys during the initial test, but were not impaired during the re-test, at which point they were only impaired when a direct comparison was made of performance at the 10-min retention interval.

In terms of the third measure that constituted the overall Z score, trials to criterion on DNMTS-1, matters are confusing. The H-ISC animals took fewer trials to acquire the DNMTS-1 than did the N animals. They took more trials to reacquire DNMTS-2 than did the N animals 6–9 months later, but recall that these reacquisition data were not used in generating the Z scores for the analysis in Zola-Morgan et al. (1994) because “more than half of the monkeys (24 of 42) obtained a score of 0 trials on this part of the task” (p. 488). There were no differences between H-RF and control monkeys in trials to criterion on the DNMTS (Alvarez et al., 1995).

What does this all amount to? What is clear from the above is that the exercise of combining four different measures of “declarative” memory to demonstrate a mild memory defect in H animals obscures the quite circumscribed nature of the “defect” that has been observed. The H-RF animals did not differ from control monkeys on any of the measures used to assess performance on the two tasks that, according to the authors, unambiguously tap declarative memory. The H-ISC animals were different on the averaged performance across three retention intervals during retest, but, as noted, they were consistently deficient only on performance of the DNMTS with a 10-min retention interval. Why does this procedural point matter? It matters because the investigators introduced a critical methodological change into the DNMTS studies when they used a 10-min retention interval, one that might account for why a deficit was observed in this case, and this case alone. When the 10-min retention interval was used, the animals were removed from the test apparatus during the retention interval and returned to their home cage. At the end of the interval they were returned to the apparatus and given the critical choice trial. This manipulation creates a new situation for the animal: Now it must not only remember the sample stimulus, it must also remember the experimental (spatial) context, and the fact that the sample is meaningful in that context. Since there is now considerable evidence that the hippocampus proper plays an essential role in memory for spatial context (Penick and Solomon, 1991; Good and Honey, 1991; Kim and Fanselow, 1992; Phillips and LeDoux, 1994; see Nadel and Willner, 1980; Nadel et al., 1985 for discussion of this issue), there is every reason to imagine that this seemingly innocent procedural manipulation had a drastic impact on the H-lesioned animals, accounting for the sudden emergence of a deficit under this condition. Normal animals would not be expected to have any problem with this additional requirement, and their performance remains well above chance at this longer interval.3

1 The “object retention” score used in these studies is actually an average across 3 days, the first of which is an acquisition rather than retention day.

2 It is worth comparing this result in a task where pure object memory is required to those obtained recently by Gaffan (1994) in a task where object-in-a-place memory was required, and in which formix lesions caused a significant impairment.

3 Alvarez et al. (1995) partially addressed this issue in the H-ELC animals, in an extra test session done after completion of the standard battery. Animals received 50 trials at each of two longer retention intervals (10 min and 40 min), and for 25 of these trials they were left in the apparatus. The authors indicate in the paper that there was no difference in the normal monkeys between the trials when they were left in the apparatus (77% correct) and the trials when they were returned to their home cage (80% correct). The fact that the normal subjects were not affected by this manipulation does not, however, address the possibility that the lesioned animals might find this “context-disruption” manipulation much more disturbing. The data from the H-ELC animals were not reported in the paper, which leaves open the possibility that the deficit in DNMTS at the longer intervals is a function of this procedural change.
This review of the data indicates that the logic underpinning the conclusion reached by Zola-Morgan et al. (1994) is not tenable. There is no mild defect in all forms of declarative memory after H lesions. There is in fact quite normal performance on several non-spatial declarative memory tasks (so defined by their correlational analyses and factor analysis), and a single, isolated deficit when the animals are subjected to a long retention interval and are required to remember the spatial context within which a task has been performed. These data are entirely consistent with the cognitive map theory of hippocampus function, but not with the declarative memory theory.

In sum, the procedure of reducing a varied set of results to a single z score would appear in this case to be inappropriate. Although it permits the pooling of data across animals and tasks and hence can increase statistical power in some cases, it is a double-edged sword at best. When one pools across tasks that might tap into quite distinct learning abilities and different underlying neural substrates, one creates the possibility of a misleading conclusion, because this very procedure presupposes that the results in the different tasks can be lumped together. That is, it presupposes that the tasks are measuring the same sort of thing. But, this is exactly what is in dispute. Until we are more clear about whether there is such a unified memory system, or whether spatial memory is quite distinct from object or fact memory, it would be best not to use procedures that lump together results from tasks tapping these varied forms of memory. Rather than supporting the declarative memory theory’s view of the hippocampus, the results from this set of studies on the effects of medial temporal lobe damage in monkeys point instead to the quite circumscribed, spatial, nature of the function of the hippocampus. A broader role in various non-spatial forms of memory is reserved for the cortical structures neighboring the hippocampus, including rhinal cortex and parahippocampal gyrus. This view has now been accepted by other workers utilizing monkey models (e.g., Mishkin and Murray, 1994), and it has serious implications for how declarative memory theory is viewed in its entirety.

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REFERENCES


4One of the authors of the paper (Squire, 1994) has recently stated that “when an animal is impaired on a behavioral task, it is difficult to relate the impairment to other impairments exhibited on other tasks” (p. 221). It is hard to reconcile such a view with the use of a single z score generated from multiple tasks and mea-