Equivalent Impairment of Spatial and Nonspatial Memory Following Damage to the Human Hippocampus

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ABSTRACT

The hippocampus has sometimes been proposed to function as a cognitive map, a memory system that stores information about allocentric space. Work with experimental animals and memory-impaired patients has raised difficulties with this view by showing that the hippocampus is not performing an exclusively spatial function. However, the possibility has remained that the hippocampus plays a special role in spatial memory or a disproportionately large role in spatial memory compared to other kinds of memory. This study compared spatial and nonspatial memory in amnesic patients with lesions of the hippocampal formation or diencephalon. Subjects studied an array of 16 toy objects and were subsequently tested for object recall, object recognition, and memory for the location of the objects. Control subjects were tested after long retention intervals in order to equate their object memory performance with that of the patients. The main finding was that, when the performance of amnesic patients on the object memory tests was matched to the object memory performance of control subjects, spatial memory performance of the amnesic patients also matched the spatial memory performance of the control subjects. The results were the same for the two groups of patients. These findings suggest that the hippocampus is not especially involved in spatial memory. Spatial memory is simply one instance of a broader category of memory that requires the hippocampus. While cognitive mapping in its most abstract sense may describe hippocampal function, our results support alternative formulations, suggesting that the hippocampus is necessary for the rapid acquisition of relational, configural, or declarative (as opposed to purely spatial) information.

Key words: amnesia, memory, diencephalon, hippocampal formation, space

Studies of human amnesic patients have long implicated the medial temporal lobe in memory functions (Von Bechterev, 1900; Scoville and Milner, 1957). Findings based on a model of human amnesia in the monkey indicate that the critical structures in this region are the hippocampal formation and adjacent, anatomically related cortex (Zola-Morgan and Squire, 1990). Although the hippocampus itself has been suspected to be an important component of the medial temporal lobe memory system, evidence that selective damage to the hippocampus can cause significant memory impairment has only recently become available. The link between memory function and the hippocampus is now supported by neuropsychological data from memory-impaired patients (Victor et al., 1961; DeJong et al., 1968; Woods et al., 1982; Cummings et al., 1984; Zola-Morgan et al., 1986; Victor and Agamanolis, 1990) as well as by studies of the effects of hippocampal formation lesions in monkeys (Mishkin, 1978; Mahut et al., 1982; Zola-Morgan et al., 1989) and hippocampal lesions in rats (Barnes, 1988; Sutherland and Rudy, 1989).

One view about the selective role of the hippocampus in memory, derived especially from behavioral studies of rats, is that the hippocampus functions as a cognitive map (O'Keefe and Nadel, 1978). According to this view, the hippocampus is a memory system that stores information about allocentric (viewpoint-independent) space. Many observations are consistent with this idea. First, in experimental animals, damage to the hippocampus produces severe deficits in spatial memory (O'Keefe et al., 1975; Olton et al., 1979; Morris et al., 1982; Sutherland et al., 1983; Barnes, 1988). In addition, “place cells” in the hippocampus discharge selectively in relation to an animal's location in space (O'Keefe and Dostrovsky, 1971; Kubie and Ranck, 1983; Foster et al., 1989). Finally, amnestic patients, including patients with presumed hippocampal damage, are impaired on spatial memory tasks (e.g., Milner, 1965; Warrington and Baddeley, 1974; Smith and Milner, 1981; Smith, 1988).

Although damage to the hippocampus produces deficits in spatial memory tasks, memory deficits are also found in tasks that are not spatial in any obvious way. For example, in the
rare, lesions of hippocampus or related structures impair performance in odor discrimination tasks, timing tasks, and configural discrimination tasks involving combinations of stimuli (Meck et al., 1984; Eichenbaum et al., 1988; Sutherland et al., 1989; Sutherland and Rudy, 1989). Similarly, monkeys with hippocampal formation lesions are impaired on recognition memory tasks for visual objects and on simple visual object discriminations (Squire and Zola-Morgan, 1983; Zola-Morgan et al., 1989). The impairment in human amnesia also extends to nonspatial material and includes difficulty in recollecting autobiographical events, facts, odors, melodies, lists, faces, and tactual impressions (Milner, 1972; Squire, 1987; Mayes, 1988). These findings, together with the finding that some kinds of learning and memory abilities are entirely spared following hippocampal lesions, led to the suggestion that spatial memory impairment in human amnesia is but one example of a broader impairment in declarative memory (Squire and Cohen, 1979; Squire 1982a).

Whereas the findings just reviewed make it clear that the mammalian hippocampus is not performing an exclusively spatial function, it remains possible that the hippocampus has a special role in spatial memory or a disproportionately large role in spatial memory compared to other kinds of memory. By this view, both spatial and nonspatial memory are affected by hippocampal damage, but spatial memory is more impaired than nonspatial memory.

In the rat, several studies of hippocampal lesions or lesions in related structures have included both spatial and nonspatial memory tasks (e.g., Aggleton et al., 1986; Morris et al., 1986; Rasmussen et al., 1989; Peirano-Manzano, 1990). In these cases performance is often impaired in the spatial task and intact in the other. However, many of the nonspatial tasks have been ones that rely on skill memory (Zola-Morgan and Squire, 1984) or habit (Mishkin et al., 1984) and do not require the integrity of the hippocampus or other components of the medial temporal lobe memory system. Few if any of the studies in rats have shown a disproportionality between two levels of impaired performance, and it is not at all clear that the spatial nature of the task is the critical dimension (Rasmussen et al., 1989).

In one study, monkeys with hippocampal formation lesions were severely impaired in the postoperative relearning of an object-place association (Parkinson et al., 1988). Simple place memory was also impaired (Angeli et al., 1988). The deficit on these spatial tasks was much more severe than was observed in earlier studies of visual object memory that involved the same lesion (Mishkin, 1978). These results therefore raised the possibility that spatial memory might be disproportionately impaired after hippocampal damage. However, when two tasks are compared, one cannot be certain that they differ only in the dimension of interest. For example, the object-place task required that correct locations of objects be recalled in the absence of external cues, while the visual object task required that a familiar object be recognized when it is presented together with a novel object. It is therefore possible that monkeys failed the object-place task because recall is more difficult than recognition, not because the task requires spatial memory.

The idea that hippocampal damage might disproportionately impair spatial memory also appears to be implicit in the view that human amnesia is due to a failure to process adequately the context of a learning episode (Kinsbourne and Wood, 1975; Winocur and Kinsbourne, 1978; Hirst, 1982; Hirst and Volpe, 1984; Mayes et al., 1985; Mayes, 1988). Contextual memory presumably includes spatial, temporal, and other information that is incidental to what is being intentionally learned. However, in amnesia, contextual memory is typically impaired together with memory for intentionally learned material (Kovner et al., 1988; Smith, 1988), and a disproportionate impairment in contextual memory has not been demonstrated, except in patients who have frontal lobe pathology in addition to amnesia (Squire, 1982b; Janowsky et al., 1989; Shimamura et al., 1990).

The purpose of the present study is to compare directly the extent of spatial and nonspatial memory impairment following hippocampal lesions. Recently, it has become practical to carry out such a study in humans because of the possibility of identifying hippocampal lesions with high-resolution magnetic resonance imaging (Press et al., 1989; Squire et al., 1990). To compare spatial and nonspatial memory performance, a method must be identified such that the relative performance of memory-impaired patients on the spatial and nonspatial tasks can be compared to the relative performance of normal subjects. One useful approach (Squire et al., 1978; Mayes and Meudell, 1981) is to equate the performance of normal subjects and amnesic patients on one of the tasks by testing the normal subjects after a suitably long retention interval. The question of interest then becomes how the two groups compare on the second task when normal subjects are tested after the same retention interval.

We have compared spatial memory and nonspatial memory using a task in which objects and their locations are learned incidentally (Smith and Milner, 1981; 1989). We tested amnesic patients with hippocampal lesions, patients with diencephalic lesions who had a similar level of amnesia, and a comparison group of normal subjects. The groups were first matched for performance on tests of object memory by testing the normal subjects at three different retention intervals. Spatial memory was then evaluated at the same retention intervals.

**EXPERIMENT 1**

**Methods**

We tested 15 amnesic patients (Table 1), 14 of whom have been studied repeatedly in our laboratory during the past few years. Patient P.H. has been studied during the past year.

**Patients with damage to the hippocampal formation**

Seven of the patients, all male, had confirmed or suspected damage to the hippocampal formation. Five patients (W.H., W.I., J.L., L.M., and P.H.) have participated in magnetic resonance imaging (MRI) studies that demonstrated marked reductions in the volume of the hippocampal formation bilaterally (Press et al., 1989; Squire et al., 1990; and unpublished observations). Patient W.H. became amnesic in 1986 during a period of at most 3 days, but without antecedent head trauma, seizure, or a known episode of unconscious-
ness. Patients J.L. and W.I. became amnesic gradually during a period of about 2 years (J.L., 1985–1987; W.I., 1983–1985); their memory impairment has remained stable since that time. Patient L.M. became amnesic in 1984 as the result of a respiratory arrest that occurred during an epileptic seizure. Patient P.H. had a 6-year history of 1–2-minute “attacks” (of possible epileptic origin) in association with gastric symptoms and transient memory impairment. In July 1989 he suffered a series of small attacks that resulted in marked and persisting memory impairment. MRI indicated reduced size of the hippocampal formation bilaterally, particularly in the posterior subportion (mean, 8.1 points lost). The average score on the Boston Naming Test was 55.1 (maximum possible, 60; range, 48–58). Scores for normal subjects on these same tests can be found elsewhere (Janowsky et al., 1989; Squire et al., 1990).

**Patients with damage to the diencephalon**

We tested eight patients with bilateral damage to midline diencephalic structures (Table 1). Seven of these patients had alcoholic Korsakoff’s syndrome (five men and two women). They had participated in either an MRI study (Squire et al., 1990) or a quantitative computed tomography (CT) study (Shimamura et al., 1988). These demonstrated marked reductions in the volume of the mammillary nuclei, reduced thalamic density, and frontal lobe atrophy. The remaining patient (M.G., female) became amnesic in 1986 following a bilateral medial thalamic infarction that was confirmed by MRI.

As a group, these patients averaged 55.5 years of age when tested and had 11.6 years of education. Their average WAIS-R IQ was 98.9. Individual IQ and Wechsler Memory Scale-Revised index scores appear in Table 1. Scores for other memory tests appear in Table 2. Note that the scores on the word recall test in Table 2 are above zero because on this test of immediate recall, several items can be retrieved from immediate memory, which is intact in amnesia. Immediate and delayed (12-minute) recall of a short prose passage averaged 5.1 and 0 segments, respectively (21 segments total; Gilbert et al., 1968). The mean score on the Dementia Rating Scale (Mattis, 1976) was 132.4 (maximum possible, 144; range, 129–136). Most of the points lost on this test were from the memory subportion (mean, 8.1 points lost). The average score on the Boston Naming Test was 55.1 (maximum possible, 60; range, 48–58). Scores for normal subjects on these same tests can be found elsewhere (Janowsky et al., 1989; Squire et al., 1990).

### Table 1. Characteristics of Amnesic Patients

<table>
<thead>
<tr>
<th>Lesion Group</th>
<th>Age (years)</th>
<th>WAIS-R IQ</th>
<th>Attention</th>
<th>Verbal</th>
<th>Visual</th>
<th>General</th>
<th>Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampal formation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.B.*</td>
<td>49</td>
<td>119</td>
<td>87</td>
<td>62</td>
<td>72</td>
<td>54</td>
<td>&lt;50</td>
</tr>
<tr>
<td>G.D.*</td>
<td>46</td>
<td>92</td>
<td>109</td>
<td>86</td>
<td>88</td>
<td>85</td>
<td>60</td>
</tr>
<tr>
<td>P.H.</td>
<td>68</td>
<td>115</td>
<td>117</td>
<td>67</td>
<td>83</td>
<td>70</td>
<td>57</td>
</tr>
<tr>
<td>W.H.</td>
<td>66</td>
<td>113</td>
<td>88</td>
<td>72</td>
<td>82</td>
<td>67</td>
<td>&lt;50</td>
</tr>
<tr>
<td>W.L.</td>
<td>76</td>
<td>104</td>
<td>92</td>
<td>72</td>
<td>82</td>
<td>71</td>
<td>58</td>
</tr>
<tr>
<td>J.L.</td>
<td>69</td>
<td>116</td>
<td>122</td>
<td>73</td>
<td>83</td>
<td>74</td>
<td>58</td>
</tr>
<tr>
<td>L.M.</td>
<td>56</td>
<td>111</td>
<td>132</td>
<td>87</td>
<td>96</td>
<td>90</td>
<td>65</td>
</tr>
<tr>
<td>Mean</td>
<td>61.4</td>
<td>110.0</td>
<td>106.7</td>
<td>74.1</td>
<td>83.7</td>
<td>73.0</td>
<td>56.9</td>
</tr>
<tr>
<td>Diencephalon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N.C.</td>
<td>43</td>
<td>90</td>
<td>62</td>
<td>80</td>
<td>60</td>
<td>69</td>
<td>&lt;50</td>
</tr>
<tr>
<td>R.C.</td>
<td>70</td>
<td>106</td>
<td>115</td>
<td>76</td>
<td>97</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>V.F.</td>
<td>67</td>
<td>103</td>
<td>101</td>
<td>78</td>
<td>72</td>
<td>72</td>
<td>66</td>
</tr>
<tr>
<td>M.G.</td>
<td>54</td>
<td>111</td>
<td>113</td>
<td>89</td>
<td>84</td>
<td>86</td>
<td>63</td>
</tr>
<tr>
<td>W.L.</td>
<td>49</td>
<td>88</td>
<td>80</td>
<td>77</td>
<td>83</td>
<td>75</td>
<td>57</td>
</tr>
<tr>
<td>D.M.</td>
<td>52</td>
<td>101</td>
<td>92</td>
<td>55</td>
<td>64</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>P.N.</td>
<td>50</td>
<td>94</td>
<td>81</td>
<td>77</td>
<td>73</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td>J.W.</td>
<td>50</td>
<td>98</td>
<td>104</td>
<td>65</td>
<td>70</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Mean</td>
<td>55.5</td>
<td>98.9</td>
<td>93.5</td>
<td>74.6</td>
<td>75.4</td>
<td>69.5</td>
<td>58.6</td>
</tr>
</tbody>
</table>

WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale Revised. The WAIS-R and each of the five indices of the WMS-R yield a mean score of 100 in the normal population, with a standard deviation of 15. The WMS-R does not provide scores for subjects who score below 50. Therefore, the three scores below 50 were scored as 50 for calculating group means.

* Although the site of lesion has not been confirmed radiologically, the etiology of the amnesia (anoxia or ischemia) suggests that damage has occurred to the hippocampal formation.
Table 2. Performance on Standard Memory Tests

<table>
<thead>
<tr>
<th>Lesion Group</th>
<th>Diagram Recall</th>
<th>Paired Associates (TO)</th>
<th>Word Recall (%)</th>
<th>Word Recognition (%)</th>
<th>50 Words</th>
<th>50 Faces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampal formation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.B.</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>33</td>
<td>83</td>
</tr>
<tr>
<td>G.D.</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>36</td>
<td>79</td>
</tr>
<tr>
<td>P.H.</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>27</td>
<td>84</td>
</tr>
<tr>
<td>W.H.</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>40</td>
<td>84</td>
</tr>
<tr>
<td>W.I.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>29</td>
<td>85</td>
</tr>
<tr>
<td>J.L.</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>40</td>
<td>93</td>
</tr>
<tr>
<td>L.M.</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>44</td>
<td>98</td>
</tr>
<tr>
<td>Mean</td>
<td>3.9</td>
<td>0.6</td>
<td>0.4</td>
<td>1.1</td>
<td>35.6</td>
<td>86.6</td>
</tr>
<tr>
<td>Diencephalon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N.C.</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>23</td>
<td>71</td>
</tr>
<tr>
<td>R.C.</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>19</td>
<td>85</td>
</tr>
<tr>
<td>V.F.</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>27</td>
<td>90</td>
</tr>
<tr>
<td>M.G.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>33</td>
<td>71</td>
</tr>
<tr>
<td>B.L.</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>88</td>
</tr>
<tr>
<td>D.M.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>32</td>
<td>56</td>
</tr>
<tr>
<td>P.N.</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>29</td>
<td>83</td>
</tr>
<tr>
<td>J.W.</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>29</td>
<td>90</td>
</tr>
<tr>
<td>Mean</td>
<td>2.8</td>
<td>0.4</td>
<td>0.1</td>
<td>1.4</td>
<td>27.5</td>
<td>79.3</td>
</tr>
<tr>
<td>Controls (N = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>20.6</td>
<td>6.0</td>
<td>7.6</td>
<td>8.9</td>
<td>71.3</td>
<td>97.6</td>
</tr>
</tbody>
</table>

Diagram recall score is based on delayed (12-minute) reproduction of the Rey-Osterrieth figure (Osterrieth, 1944; maximum score = 36); average score for copying the figure was 27.3, a normal score (Kritchevsky et al., 1988); paired associate scores are the number of word pairs recalled on three successive trials (maximum score = 10/trial); word recall score is the percentage of words identified correctly across five successive study-test trials (Rey, 1964); word recognition score is the percentage of words identified correctly by yes/no recognition test across five successive study-test trials; score for words and faces is based on a 24-hour recognition test of 50 words or 50 faces (modified from Warrington, 1984; maximum score = 50, chance = 25). The mean scores for normal control subjects shown for these tests are from Squire and Shimamura (1986).

Materials

The test was based on one described by Smith and Milner (1981). A set of 16 small toys were used as test objects (house, telephone, television, scissors, tennis racquet, turtle, coat, chair, car, typewriter, watch, wrench, teacup, pail, spoon, and saxophone). Three practice toys were also selected (sunglasses, clipboard, and guitar). Sheets of paper 60 cm square (blank newsprint) were used as the background upon which the objects appeared. Finally, a written 8-choice, 16-item recognition memory test for the names of the objects was prepared that included distractor items similar to the test objects.

Procedure

Prior to testing, the 16 toys were distributed on the paper background, which was placed on a table (Fig. 1). The only constraints were that the toys should be evenly but randomly distributed on the paper and that there be no obvious relationship among neighboring objects. A different spatial arrangement of the objects was used for each subject. Each object was lightly outlined on the paper so that the original location for each object could be reconstructed at the end of

segments, respectively (21 segments total). The mean score on the Dementia Rating Scale (Mattis, 1976) was 131.0 (maximum possible, 144; range, 119–143), with 6.2 points lost from the memory subportion of the test and 3.9 points lost from the initiation-perseveration subportion. The average score on the Boston Naming Test was 54.1 (maximum possible, 60; range, 48–57).

Healthy control subjects

A total of 28 control subjects were tested (11 men and 17 women). They were either volunteers or employees at the Veterans Affairs Medical Center or recruited from the UCSD retirement community. They were selected to match the 15 amnesic patients with respect to age (mean, 60 years; range, 43–78), education (mean, 14.5 years; range, 11–19), and 2 WAIS-R subtest scores. Information (control subjects, mean, 21.6; 15 amnesic patients, mean, 20.0) and Vocabulary (control subjects, mean, 54.0; 15 amnesic patients, mean, 52.4). Immediate and delayed (12-minute) recall of a short prose passage averaged 8.1 and 6.8 segments, respectively. The 28 subjects were tested at one of three intervals after initial learning (5-minutes, n = 8; 1–2 weeks, n = 8; 3–5 weeks, n = 12. see Procedure).
testing. To begin, the array of toys was covered and instructions were given using the three practice objects. Subjects sat facing the array. They were told that this was a test of their ability to estimate prices and that they would be estimating the real price of objects represented by toys. They were then given a pencil to point to each object and were asked not to touch them. Subjects then began with the practice objects, first naming an object and then giving a price for the real object it represented.

When the instructions were clear, the array of 16 toys was revealed and the subject was asked to name and price each toy in any order. The experimenter noted the name given each object and corrected any names that were not as they would later appear on the recognition test. The price estimates were also recorded. The experimenter prompted or slowed subjects such that they spent approximately 10 seconds studying each object. When all 16 objects had been evaluated, the experimenter quickly removed the toys and the paper background sheet, giving no indication that there would be further testing. Then, following a scheduled delay (5 minutes for the amnesic patients, 5 minutes to 5 weeks for the control subjects), the retention phase of the experiment was administered. For subjects tested after a 5-minute delay, the interval was spent in unrelated conversation.

The retention test consisted of three parts: recall of object names, recognition of object names, and spatial recall. First, subjects were asked to recall all of the objects that they had seen during the pricing task. Two minutes were allowed for recall. Next, a written 8-choice, 16-item recognition test was administered. Subjects were given as much time as they needed to complete this test. Finally, subjects were provided with a new background paper sheet and the original 16 toys, with the instructions to place each toy on the paper exactly where it had been located during the pricing task. After the subject had replaced all of the objects, their locations were outlined in pencil for later comparison with the original study locations.

**Scoring**

The number of object names correctly recalled, the percentage of object names correctly recognized, and two measures of spatial recall were calculated for each subject.

**Absolute spatial recall**

This method, adopted from Smith and Milner (1981), involved measuring the absolute distance (cm) between the location of each object at the time of the price estimation task and the location in which it was subsequently placed by the subject. To obtain this measure, the two pieces of paper showing outlines of the objects were superimposed so that they were in the same orientation with respect to where the subject had been seated. The straight-line distances between the centers of each outlined object were then measured and averaged. In this way an absolute displacement score was obtained for each subject.

**Relative spatial recall**

A second measure was used in order to determine how well subjects remembered the arrangement of the objects relative to one another, independently of their absolute location on the table. To obtain this measure, x- and y-axes were first
placed through one of the objects in the original study array. Every other object in the array was then assigned a value (1, 2, 3, or 4), corresponding to which quadrant it was located in relative to the first object (above it and to the left, above it and to the right, and so on). This procedure was then repeated for all 16 objects in the array, resulting in a half-matrix of 120 quadrant measures that described the spatial relationship of each object to every other object in the array. Finally, the entire procedure was repeated using the array of objects that was constructed by the subject during the spatial recall test. The relative spatial recall measure was derived by calculating how many times the same quadrant relationship existed between pairs of objects at study and at test. This measure was expressed as a percentage (number of times that the quadrant relationship was correct out of a maximum of 120).

**Determination of baseline spatial recall**

A group of 20 healthy subjects (mean age, 27.9; range, 20–43), who were volunteers or employees at the Veterans Affairs Medical Center, participated in a control condition to determine baseline (random) performance in the spatial memory task. These subjects were given the 16 toys and a blank sheet of paper and were asked to place the toys on the paper in any way that they chose. They were given no further instructions or explanation. Scores were then obtained by evaluating the array constructed by each subject against a study array that had been presented to an amnesic patient. Each of the 20 arrays constructed by the normal subjects was randomly paired with one of the 15 arrays presented to the patients (10 of the study arrays that had been given to patients were used once in these pairings, and 5 were used twice). Both absolute and relative measures of spatial recall were calculated in this way to provide measures of baseline, random performance on the spatial recall task.

**Results**

The two groups of amnesic patients were compared with control subjects who were tested after retention delays of 5 minutes, 1–2 weeks, and 3–5 weeks. The amnesic patients and the control groups were first compared with respect to item recall and item recognition to determine the severity of memory impairment in the amnesic patients. We then examined spatial memory performance to determine how the amnesic patients performed in relation to what would have been expected based on their recall and recognition memory performance. For statistical analysis of the recall, recognition, and spatial scores, we performed separate one-way ANOVAs with planned comparisons. The results were identical when the pairwise comparisons were performed by *t*-tests.

**Recall**

The two groups of amnesic patients were first compared to the control subjects who were tested at the same (5-minute) retention interval (Fig. 2A). Both groups of patients, those with damage to the hippocampal formation and those with diencephalic damage, were significantly impaired (*P < .001*) and could recall an average of only 2.7 and 3.6 objects, respectively, of the 16 objects that had been presented. The control subjects recalled 9.2 objects. Both groups of amnesic patients also performed more poorly than the control subjects who were tested after a 1–2-week delay (5.9 objects recalled, *P < .05*). The performance of the two patient groups was similar to that of control subjects tested after a retention delay of 3–5 weeks (4.2 objects recalled, *P > .10*).

**Recognition**

Results from the recognition test were virtually the same as for recall (Fig. 2B). Both groups of amnesic patients performed much more poorly than the control subjects tested after the 5-minute delay (*P < .001*). Patients with damage to the hippocampal formation recognized 53.7% of the objects, patients with diencephalic lesions recognized 59.5% of the objects, and the control subjects recognized 98.4% of the objects. The patients also performed more poorly than control subjects who were tested after a 1–2-week delay (81.4% cor-
rect for the control subjects, $P < .05$). As was the case for recall, the performance of the two groups of amnesic patients was similar to that of the control subjects who were tested after a 3-5-week delay (58.9% correct for the control subjects, $P > .2$).

The recall and recognition tests thus showed that the two groups of patients performed similarly to control subjects who were tested after a retention delay of 3-5 weeks. The patients with damage to the hippocampal formation did perform numerically more poorly than the patients with diencephalic damage, but this difference did not approach significance for either recall or recognition ($P > .2$).

**Spatial recall**

The question of interest was whether the spatial memory performance of amnesic patients was, like recall and recognition performance, similar to the performance of control subjects who were tested after a 3-5-week delay or whether the spatial memory performance of amnesic patients was poorer than the performance of these control subjects.

We first considered the results obtained using the absolute spatial memory measure (Fig. 3A). Both groups of amnesic patients were severely impaired at spatial recall. The patients with damage to the hippocampal formation and those with diencephalic damage located the 16 objects on an average of 21.7 cm and 16.8 cm, respectively, from their correct positions. The control subjects who were tested after the same 5-minute delay as the amnesic patients obtained a score of 9.5 cm, significantly better than the scores obtained by the patients ($P < .01$). The control group tested after a 1-2-week delay (19.4 cm displacement) performed similarly to the patients ($P > .2$). The control group tested after a 3-5-week delay obtained a displacement score (22.1 cm), similar to the score of the patients with damage to the hippocampal formation ($F < 1$) and worse than the score of the patients with diencephalic damage ($P < .05$). The difference between the two patient groups did not reach statistical significance ($F[1,38] = 3.4, P = .07$). Indeed, a similar numerical difference was observed for the two groups on the measures of recall and recognition memory. Finally, the two groups of amnesic patients and all three control groups performed significantly better ($P < .01$) than the baseline score (26.4 cm) obtained by subjects who placed objects on the background sheet without having seen them previously.

We next considered the results obtained with the relative location measure (Fig. 3B). In most respects the findings for the relative measure of spatial memory were the same as for the absolute measure. Both patient groups were severely impaired ($P < .001$) when compared with control subjects tested after a 5-minute delay (36.8% and 47.9% correct for the hippocampal and diencephalic groups, respectively; 73.1% correct for the control group). The patients with hippocampal damage were not statistically distinguishable from either the control group tested after 1-2 weeks (45% correct, $P > .2$) or the control group tested after a delay of 3-5 weeks (31% correct, $F < 1$). The patients with diencephalic damage performed similarly to the control subjects tested after a delay of 1-2 weeks ($F < 1, P > .2$) and better than the control subjects tested after a delay of 3-5 weeks ($P < .05$). The performance of both groups of amnesic patients was better ($P < .001$) than the baseline score (24.0% correct) that was obtained by the subjects who placed objects in an array without having encountered them previously. Two of the control groups (the 5-minute and 1-2-week delay groups) also performed better than baseline ($P < .001$). The control group tested after a 3-5-week delay performed only marginally better than the baseline score ($t[25] = 1.89, P = .07$).

Finally, the patients with diencephalic damage performed numerically better than patients with hippocampal damage, but this difference did not approach significance ($F[1,38] = 2.5, P > .10$). Thus, a small numerical difference between the patients with hippocampal damage and those with dience-
phalic damage was consistently observed in the tests of recall and recognition and in both measures of spatial memory.

Discussion

Experiment 1 was designed to determine whether memory for spatial information is disproportionately affected by hippocampal lesions. We first matched the performance of control subjects and amnesic patients (seven with hippocampal lesions and eight with diencephalic lesions) on two tests of object memory: recall of object names and recognition of object names. On these tests, control subjects performed similarly to the amnesic patients when the retention interval for the control subjects was 3–5 weeks and the retention interval for the amnesic patients was 5 minutes. If spatial memory were disproportionally impaired, then the amnesic patients should have performed worse than the control subjects on the test of spatial memory. We found that performance of the amnesic patients on the spatial memory test was about what would have been expected given their level of object memory performance. The results were the same for patients with diencephalic lesions as for the patients with damage to the hippocampal formation.

It is important to note that each subject group performed significantly above baseline (chance) levels on the spatial memory test ($P < .01$). Above-chance performance is essential if meaningful comparisons are to be made between two groups of scores. Because of the importance of this issue, we also considered whether individual amnesic patients performed the spatial memory test at above-chance levels. We determined that six of the patients with diencephalic lesions (all but N.C. and D.M.) and two of the patients with hippocampal lesions (G.D. and L.M.) scored more than 2 standard deviations outside the mean of the baseline control group (i.e., the group used to establish baseline, chance performance levels). For the five other patients with hippocampal lesions, we obtained a more reliable spatial memory score by administering the spatial memory test on three additional occasions separated by at least 1 week. For each test, the objects were presented in a new array of the data. The results were that two of the patients (W.H. and P.H.) now performed significantly better than the mean score produced by the baseline control group (one-group $t$-tests, $P < .05$; these calculations were based on the relative location measure). The mean scores of the patients did not noticeably change as a result of multiple testing. Multiple testing simply provided a measure of variability, thereby permitting each patient to be compared individually to the baseline control mean. Thus, the majority of individual amnesic patients (six of eight patients with diencephalic lesions and four of seven patients with hippocampal lesions) did perform above chance levels on the spatial memory test, and these findings strengthen the conclusion based on the group scores that the amnesic patients did not have disproportionately impaired spatial memory.

One potential complication is that the object memory tests in experiment 1 were based on memory for objects that had been presented in a spatial array. If subjects used spatial strategies to recall and recognize objects from the array, then the object memory tests in experiment 1 would to some extent be tests of spatial memory. Accordingly, one could suppose that the patients performed poorly on the memory tests in experiment 1 because all three tests (the two object memory tests as well as the spatial memory test) depended importantly on the use of deficient spatial memory strategies.

EXPERIMENT 2

We considered this possibility in experiment 2 by presenting objects individually in one location instead of in an array. Recall and recognition for the names of the objects were subsequently tested exactly as in experiment 1. This method allowed object memory to be assessed in a way that minimized the utility of spatial strategies. If the amnesic patients performed poorly on the object memory tests in experiment 1 because the objects had been presented in a spatial array, and if spatial memory is especially deficient in amnesia, then under sequential viewing conditions the object memory performance of amnesic patients should improve relative to the performance of the control subjects who were tested after a 3–5-week retention interval.

Methods

Amnesic patients

The same 15 patients described in experiment 1 were tested in experiment 2.

Healthy control subjects

A total of 20 control subjects were tested, drawn from the same population as in experiment 1. Subjects were assigned to one of two groups to be tested at different retention intervals (1–2 weeks, $n = 8$; 3–5 weeks $n = 12$). The 20 control subjects averaged 60.6 years of age and had 14.1 years of education. Their average score on the Information subtest of the WAIS-R was 21.0 (15 amnesic patients = 20.0) and their average score on the Vocabulary subtest was 53.9 (15 amnesic patients = 52.4). Immediate and delayed recall (12 minutes) for the short prose passage averaged 7.9 and 6.2 segments, respectively.

Materials

A set of 16 new toys were used as test objects (clarinet, pitcher, calculator, football, brush, sailboat, hammer, shirt, phonograph, necklace, mixer, bowl, telescope, bicycle, table, and goose). The practice objects were the same as those used in experiment 1. An 8-choice, 16-item recognition memory test was also constructed as described in experiment 1.

Procedure

The test began with the same instructions used in experiment 1. Subjects were told that they would be asked to estimate the average price of real objects represented by toys. As before, they began with the practice objects and then moved to the test objects. In this experiment, rather than presenting the objects in an array, each object was presented to the subject in the center of an 8½ × 11-inch sheet of white paper for 10 seconds. The subject named the object and gave a price for its real equivalent. The names and prices were recorded by the experimenter. When all of the objects had been evaluated, the delay period began, but no indication was given that there would be further testing. As in experiment
1, the retention interval for amnesic patients was 5 minutes and for control subjects was 1–5 weeks. At the end of the retention interval, recall and recognition memory for the objects was tested exactly as in experiment 1.

Results

Amnesic patients and control subjects performed more poorly on the recall and recognition tests of experiment 2 than they did on the recall test of experiment 1. One important difference in the two experiments was that all of the objects in experiment 1 were in view throughout the 2–3-minute period needed to perform the pricing task. In experiment 2, each object was in view for only 10 seconds. Whatever factors made these tasks more difficult, the important question concerned the relative performance of amnesic patients and control subjects in experiment 2.

Recall

Both groups of amnesic patients performed more poorly than the control subjects who were tested after a retention interval of 1–2 weeks (Fig. 4A). The control subjects recalled 3.7 objects, but the patients with hippocampal damage or diencephalic damage could recall only 0.9 and 1.6 objects, respectively ($P < .05$). As in experiment 1, the amnesic patients performed similarly to the control subjects who were tested after a delay of 3–5 weeks (1.8 objects recalled, $P > .2$). Thus, despite the fact that this recall task eliminated the possible use of spatial strategies for recall, the relative performance of amnesic patients and control subjects was the same as it was in experiment 1.

Recognition

The pattern of results for recognition memory was exactly as was observed for recall. Both groups of amnesic patients performed more poorly than the control subjects who were tested after a retention interval of 1–2 weeks (Fig. 4B). The control subjects recognized 71.3% of the objects, but the hippocampal and diencephalic groups could recognize only 50.9% and 53.9% of the objects, respectively (hippocampal group vs. control group: $F[1, 31] = 3.8$, $P = .06$; diencephalic group vs. control group: $F[1, 31] = 2.9$, $P = .10$). There was no detectable difference between the performance of the patients and the control subjects tested after a delay of 3–5 weeks (43.2% correct for the control subjects, $P > .2$). Thus, for recognition memory, the relative performance of amnesic patients and control subjects was the same as it was in experiment 1.

Discussion

Experiment 2 was designed to evaluate the possible importance of spatial strategies for the object memory tasks used in experiment 1. In experiment 1, the objects were presented in a spatial array; in experiment 2, they were presented sequentially in a single location. If spatial memory is especially impaired in amnesia and if deficient spatial memory strategies contributed to the poor performance of amnesic patients on the object memory tests of experiment 1, then minimizing the spatial aspects of the test should improve the performance of amnesic patients in comparison to control subjects. However, the results were that, just as in experiment 1, the performance of the amnesic patients on the recall and recognition tests matched the performance of the control subjects who were tested following a retention interval of 3–5 weeks. Accordingly, it is unlikely that experiment 1 obscured a disproportionately severe spatial memory impairment by using object memory tests that depended as much on spatial strategies as the spatial memory tests.

GENERAL DISCUSSION

We tested amnesic patients with hippocampal or diencephalic lesions to determine the severity of their memory impairment for spatial information. It has long been appreciated that the memory impairment associated with these lesions is not exclusively spatial. The question of interest was whether...
memory for spatial information is worse than would be expected, given the level of memory impairment for other kinds of (nonspatial) information. In experiment 1, we presented 16 objects in a spatial array and later tested object recall, object recognition, and memory for the location of the objects. Control subjects were tested at long delays after they had interacted with the objects, in order to determine what level of spatial memory performance should be expected given particular levels of (weak) memory for the objects. The main finding was that when the performance of amnesic patients on the object memory tests was matched to the object memory performance of control subjects, the spatial memory performance of the amnesic patients also matched the spatial memory performance of these control subjects. In other words, memory for the spatial locations of the objects was no worse than memory for the names of the objects. In experiment 2, we presented objects sequentially in a single location instead of in a spatial array and found that the relative performance of amnesic patients and control subjects on object recall and recognition was the same as in experiment 1. This result shows that the object memory tests in experiment 1 did not depend importantly on spatial strategies. Thus, for amnesic patients the level of impaired performance on a memory test for the spatial location of objects (i.e., a test with a critical spatial component) was about what should have been expected from their level of impaired performance on a memory test that had no spatial component (i.e., in experiment 2).

These results would seem to argue against the notion that the hippocampus is performing a particularly spatial function. Amnesic patients with hippocampal lesions performed no more poorly on spatial memory tests than they did on nonspatial memory tests. Moreover, the pattern of findings exhibited by patients with hippocampal lesions was recapitulated by amnesic patients with diencephalic lesions. It should be noted that the original formulation of cognitive mapping theory (O'Keefe and Nadel, 1978) distinguished between the functions of the left and right human hippocampus. Specifically, the right hippocampus in humans was proposed to subserve a cognitive mapping function similar to that proposed for experimental animals. The left hippocampus was proposed to subserve a more abstract mapping function involving a linguistic framework to organize narratives. Accordingly, cognitive mapping theory in its strictly spatial sense is properly applicable only to the right hippocampus of humans. Our patients did have damage to the right hippocampus (as well as to the left) and therefore are appropriate subjects for testing the spatial aspects of the cognitive mapping hypothesis. We used a spatial memory test sensitive to right hippocampal damage (Smith and Milner, 1981). Moreover, object recall (a nonspatial memory task) is also sensitive to right (as well as to left) hippocampal damage (Smith and Milner, 1981). That is, both our spatial and nonspatial tasks are sensitive to right hippocampal damage, so that the tasks were appropriate for detecting differences in levels of impaired performance. Instead, we found that hippocampal damage produced no greater spatial memory impairment than nonspatial memory impairment. In addition, hippocampal lesions produced no greater impairment on either task than did diencephalic lesions.

These findings add to a growing body of work suggesting that the role of the hippocampus in memory is not uniquely spatial. Performance on spatial memory tasks can be severely impaired after hippocampal lesions and lesions of related structures. However, performance on nonspatial tasks can also be impaired, including, for example, odor discrimination learning (Eichenbaum et al., 1988), timing tasks (Meck et al., 1984), negative patterning discrimination (Sutherland and Rudy, 1989), and visual object recognition tasks (Squire and Zola-Morgan, 1983). Nevertheless, studies comparing spatial and nonspatial memory, especially in rats with hippocampal lesions, have often reported that performance was impaired on spatial tasks and spared on nonspatial tasks. For many years, it was possible to interpret this pattern of results as favoring an important role for the hippocampus in spatial memory functions. However, studies of experimental animals with hippocampal lesions (Hirsh, 1974; Mishkin et al., 1984; Zola-Morgan and Squire, 1984; Eichenbaum et al., 1989; Packard et al., 1989; Sutherland and Rudy, 1989) and studies of human amnesic patients (Cohen and Squire, 1980; Squire, 1982a; Schacter, 1987; Weiskrantz, 1987) led eventually to an alternative interpretation, namely that performance was spared on certain tasks not because they are nonspatial but because these tasks depend on a larger class of memory abilities that operate independently of the hippocampus (variously termed habit, simple associative memory, implicit memory, or nondeclarative memory). At the same time, this formulation accommodates the finding that performance on many nonspatial tasks is impaired by hippocampal lesions by supposing that all such tasks require a kind of memory that depends on the hippocampus (variously termed cognitive, representational, configurational, relational, or declarative).

By this view, the hippocampus is not dedicated to spatial memory. Rather, spatial memory tasks are simply one example of a broader category of tasks that require the hippocampus (Squire, 1979; Rasmussen et al., 1989). The hippocampus, and the system to which it belongs, is essential for the acquisition of relationships, combinations, and conjunctions among stimuli (Eichenbaum et al., 1988; Sutherland and Rudy, 1989; Squire et al., 1989). The resulting representation is flexible and available to multiple response systems (Cohen, 1984; Squire, 1987). Simple associations between stimuli and responses can be acquired without this system. In these cases, what is learned is relatively inflexible, and the knowledge gained can be expressed in a limited context and only through the same response systems that participated in original learning (Eichenbaum et al., 1989; Saunders and Weiskrantz, 1989; Eichenbaum et al., 1990). Spatial memory is exemplary of the kind of information usually dependent on the hippocampus. Thus, it has been suggested that to acquire spatial information, conjunctions of multiple distal cues and movement information must be acquired in relationship to each other (McNaughton et al., 1989). In its most abstract sense, cognitive mapping may be a reasonable description of the important role the hippocampus plays in relating various stimuli to each other and in establishing a flexible representation. The hippocampus may bind together the distributed sites in neocortex that together form a memory of a whole event. However, in humans, and most probably in other animals, the hippocampus is not functioning in an especially
spatial way, as implied by the strict sense of the cognitive mapping hypothesis.

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