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Impaired Transverse Patterning in Human Amnesia Is a Special Case of Impaired Memory for Two-Choice Discrimination Tasks

Jonathan M. Reed
University of California, San Diego

Larry R. Squire
Veterans Affairs Medical Center, San Diego
and University of California, San Diego

Three amnesic patients with damage limited to the hippocampal formation, a severely amnesic patient with extensive medial temporal lobe damage, and 9 controls were tested on the transverse patterning problem (A + B−, B + C−, and C + A−) and also on 2 control problems. One of the control problems was matched to the transverse patterning problem with respect to the number of pairwise decisions that were required. The 2nd control problem was matched to the transverse patterning problem with respect to the number of trials needed by controls to learn the task. The amnesic patients were impaired at solving both the transverse patterning problem and the control problems. The findings suggest that impaired learning of the transverse patterning problem by amnesic patients derives from their general impairment in declarative memory, which affects performance on most 2-choice discrimination tasks.

The hippocampus and surrounding medial temporal lobe cortices play an important role in memory (Mishkin & Murray, 1994; Scoville & Milner, 1957; Squire & Zola-Morgan, 1991; Suzuki, 1996). Amnesic patients with bilateral damage to these structures exhibit impaired declarative (explicit) memory but intact nondeclarative (implicit) memory (Schacter, Chiu, & Ochsner, 1993; Squire, Knowlton, & Musen, 1993). To date, the distinction between declarative and nondeclarative memory has been based mainly on three criteria: (a) whether or not memory is impaired in amnesia, (b) whether or not memory performance depends on conscious recollection, and (c) whether memory performance supports the acquisition of flexible representations that can be used to make relational judgments (e.g., having learned that A > B and B > C, one can infer that A > C; Cohen, 1984; Eichenbaum, 1997; Reber, Knowlton, & Squire, 1996). Declarative memory can be flexibly applied to new situations, whereas nondeclarative memory is less flexible and best assessed in contexts similar to those of the original learning.

An alternative distinction between hippocampal and nonhippocampal memory functions has been developed by Rudy and Sutherland (Rudy & Sutherland, 1992, 1994; Sutherland & Rudy, 1989). They proposed that the hippocampal formation (the CA fields of the hippocampus, the dentate gyrus, the subicular complex, and the entorhinal cortex) is essential for establishing configural associations, whereas nonhippocampal memory can support only the development of nonconfigural, elemental associations. An elemental association is formed when a discrete cue (e.g., A) is associated with a response (X; e.g., A-X). By contrast, a configural association is formed when multiple cues (e.g., A and B) are combined to form a single representation (e.g., AB) that can then be associated with a response (e.g., AB-X). An important source of evidence for the configural association view of hippocampal function comes from studies of the transverse patterning problem.

The transverse patterning problem involves three stimuli (A, B, and C), two of which are presented on each trial. Subjects are rewarded according to the following scheme: A is rewarded when presented with B (A + B−); B is rewarded when presented with C (B + C−); and C is rewarded when presented with A (C + A−). Because each stimulus element of the transverse pattern is rewarded equally often, the problem cannot be solved by elemental associations. Instead, the cues A, B, and C must be represented configurally as AB, BC, and CA, and each of these configurations must then be uniquely associated with the appropriate response.

Transverse patterning problems can be learned by normal pigeons (Couvillon & Bitterman, 1996; Wynne, 1996), rats (Alvarado & Rudy, 1992, 1995a, 1995b; Dusek & Eichenbaum, 1998), monkeys (Alvarado, Wright, & Bachevalier, 1995), and humans (Rickard & Grafman, 1998; Rudy, Keith, & Georgen, 1993). Consistent with the idea that the hippocampal formation is required to form configural associations, lesions of the hippocampal formation in rats (Alvarado & Rudy, 1995a, 1995b; Dusek & Eichenbaum, 1998), monkeys (Alvarado et al., 1995), and humans (Rickard & Grafman, 1998) impaired learning of the transverse

Jonathan M. Reed, Department of Psychiatry, University of California, San Diego; Larry R. Squire, Research Service, Veterans Affairs Medical Center, San Diego and Departments of Psychiatry and Neurosciences, University of California, San Diego.

Jonathan M. Reed is now at the Department of Psychology, East Carolina University, Greenville, North Carolina.

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Correspondence concerning this article should be addressed to Larry R. Squire, Veterans Affairs Medical Center 116A, 3350 La Jolla Village Drive, San Diego, California, 92161. Electronic mail may be sent to lsquire@ucsd.edu.

patterning problem. However, in other studies with rats, hippocampal lesions have not consistently impaired learning of either the transverse patterning problem (Bussey, Warburton, Aggleton, & Muir, 1998) or other problems that supposedly require the formation of configural associations (Davidson, McKernan, & Jarrard, 1993; Gallagher & Holland, 1992; Han, Gallagher, & Holland, 1998).

One difficulty in evaluating the idea that configural associations require the hippocampal formation is that it is not always obvious what strategy an animal will apply to a particular problem. For example, Alvarado and Rudy (1992) found that when a single ambiguous element was included in a simple two-discrimination problem (A + B−, B +C−), rats formed configural representations of the problem even though elemental representations would have been sufficient. On the other hand, elemental solutions may exist for problems that by definition have been described as configural tasks (Davidson et al., 1993). These considerations suggest that logical analysis of a task may not be as informative as determining how an animal actually approaches the problem.

Two-choice discrimination tasks, which are the building blocks of the transverse patterning problem, illustrate the issue. A large body of literature documents the fact that rats with hippocampal formation lesions acquire and retain many two-choice discrimination problems as well as intact rats do (for reviews, see Gray & McNaughton, 1983; O'Keefe & Nadel, 1978; for later studies, see Dusek & Eichenbaum, 1997; Eichenbaum, Fagan, & Cohen, 1986). However, when a two-choice discrimination problem places a premium on remembering relational information and making direct comparisons between stimuli, rats with hippocampal formation lesions are impaired (see Eichenbaum et al., 1986). The findings for monkeys also depend on the nature of the task. When a two-choice discrimination problem is one that can be learned rapidly by intact monkeys, monkeys with hippocampal formation lesions are impaired at learning and retention. However, the same monkeys perform well when the task is difficult and is learned only gradually by intact monkeys (Squire & Zola-Morgan, 1983; Zola, Teng, Clark, Stefanacci, Buffalo, & Squire, 1998; Zola-Morgan, Squire, & Amaral, 1989). It has been suggested that monkeys learn difficult discrimination tasks gradually, in much the same way that they learn skills (Iversen, 1976; Squire & Zola-Morgan, 1983). Finally, amnesic patients are typically impaired at two-choice discrimination problems (Oscar-Berman & Zola-Morgan, 1980; Squire, Zola-Morgan, & Chen, 1988). They may be able to learn the problem if trials are spaced closely together, but they cannot later remember which object is correct.

This body of data can be understood if it is supposed that experimental animals with hippocampal lesions succeed at many two-choice discrimination problems because they readily engage a nonhippocampal, habit-learning strategy and do not learn about the objects in relation to any other objects or context (Hirsh, 1974; Mishkin & Petri, 1984). In contrast, humans have a declarative strategy that is well suited for two-choice discrimination problems, and they proceed essentially by quickly memorizing which stimulus is the "correct" one. In fact, humans may engage a habit strategy only when the discrimination problem must be acquired slowly and when the associations between the stimulus elements and the responses are difficult to memorize (see Knowlton, Mangels, & Squire, 1996).

If this view is correct, then amnesic patients not only should have difficulty mastering the three-part transverse patterning problem, but also should have difficulty with any set of three elemental discrimination problems. A set of three unrelated problems may not be as difficult as the three-part transverse patterning problem because the unrelated problems do not contain overlapping elements. However, if one constructs a larger set of elemental problems, which control subjects have as much difficulty learning as the transverse patterning problem, then amnesic patients should be as impaired on this set of elemental problems as on the transverse patterning problem.

We tested 3 amnesic patients with damage limited to the hippocampal formation (AMN), 1 severely amnesic patient with extensive medial temporal lobe damage, and 9 controls (CON). All participants were tested on the transverse patterning problem and two control problems. One control problem, a three-pair concurrent learning problem, was matched to the transverse patterning problem with respect to the number of pairwise decisions it required. The second control problem, a six-pair concurrent learning problem, was matched to the transverse patterning problem with respect to the number of trials that controls needed to meet the learning criterion.

Method

Participants

Amnesic patients. Four amnesic patients were studied, 3 men and 1 woman. Three of the patients had lesions limited to the hippocampal formation (A.B., P.H., and L.J.), and the other patient (E.P.) had extensive bilateral damage to the medial temporal lobe. Patient A.B. was unable to participate in magnetic resonance imaging studies because he wore a pacemaker. He became amnesic in 1975 after an anoxic episode associated with cardiac arrest and is presumed to have hippocampal damage on the basis of this etiology. For patients P.H. (Polich & Squire, 1993) and L.J. (Reed & Squire, 1998), magnetic resonance imaging identified bilateral hippocampal damage. Patient P.H. (Polich & Squire, 1993) had a 6-year history of 1- to 2-min attacks (with a possible epileptic basis) that were associated with gastric symptoms and transient memory impairment. In July 1989, he suffered from a series of brief episodes, after which he had a marked and persistent memory loss. Patient L.J. became amnesic with no known precipitating event during a 6-month period that began in late 1988. Her memory impairment has remained stable since that time. Patient E.P. developed profound anterograde and retrograde amnesia in 1992 after contracting herpes simplex encephalitis. Neuroimaging studies revealed large lesions of the medial temporal lobe (Reed & Squire, 1998). The damage involves the amygdaloid complex, the hippocampal region (CA fields, dentate gyrus, and subicular complex), and the entorhinal, perirhinal, and parahippocampal cortices (Buffalo, Reber, & Squire, 1998). E.P.'s damage is primarily medial temporal but also involves the laterally adjacent

Table 1
Characteristics of Amnesic Patients

Patient	Year of birth	Education (years)	WAIS-R IQ	WMS-R				
				Attention	Verbal	Visual	General	Delay
A.B.	1937	20	104	87	62	72	54	<50
P.H.	1922	19	118	117	67	83	70	57
L.J.	1937	12	98	105	83	60	69	<50
E.P.	1922	12	101	94	59	92	68	56

Note. The Wechsler Adult Intelligence Scale–Revised (WAIS-R) and the Wechsler Memory Scale-Revised (WMS-R) yield mean scores of 100 in the normal population, with standard deviation of 15. The WMS-R does not provide numerical scores for individuals who score below 50.

fusiform gyrus at some levels. Neuropsychological data for the 4 patients are presented in Table 1 and Table 2. It should be noted that all 4 patients exhibit amnesia despite having obtained intelligence scores within the normal range.

Controls. The 9 controls (8 men and 1 woman) were volunteers and employees at the San Diego Veterans Affairs Medical Center, San Diego, California. They were matched to the 3 patients with lesions of the hippocampal formation. As a group they averaged 66.6 years of age and 15.7 years of education. They scored 23.1 and 56.4, respectively, on the Information and Vocabulary subscales of the Wechsler Adult Intelligence Scale–Revised (22 and 58 for the 3 patients with hippocampal formation lesions).

Materials and Procedure

Stimulus materials were a pool of 21 different geometric shapes constructed to be unique and easily discriminable (Figure 1). For each participants 3 shapes (A, B, and C) were randomly selected from the pool for use with the transverse patterning problem, 6 shapes (D, E, F, G, H, and I) were selected for the three-pair concurrent learning problem, and 12 shapes (J through U) were selected for the six-pair concurrent learning problem. Each shape was used only once for each participant. For the concurrent pair problems, half of the selected shapes were randomly designated as correct (+), and the others were designated as incorrect (−). All testing was completed in 1998 with a Cannon Innova Book 490CDS laptop computer.

Patient E.P. was tested twice. On the first occasion he attempted to solve the transverse patterning problem, and on the second occasion he attempted to solve the three-pair concurrent problem. The other patients and the controls were tested on three occasions separated by at least 2 weeks. During the first session, participants attempted to solve the transverse patterning problem. During the second and third sessions, they attempted to solve the three-pair concurrent and six-pair concurrent problems, respectively.

Participants received the same instructions at the beginning of each test session. They were told that they would see two shapes on each trial and that they should try to choose the correct shape. Each test session began with eight practice trials involving a circle and a triangle, and the choice of the circle was rewarded. These shapes were not used for any of the experimental problems. The eight trials were repeated a second time for participants who had any difficulty. An index card with printed instructions was kept in view at all times.

After the practice trials were completed, testing with one of the three problems began. A trial began when two different shapes appeared on the screen with an arrow cursor. The shapes appeared on each side of the center of the screen, and the cursor appeared in the center. Participants indicated their choice by moving the cursor to one of the shapes. They were allowed as much time as they

Table 2
Performance on Standard Memory Tests

Patient	Diagram recall	Paired associates			Word recall (%)	Word recognition (%)	50 words	50 faces
		Trial 1	Trial 2	Trial 3				
A.B.	4	1	1	1	33	82.7	32	33
P.H.	3	0	0	1	31	81.3	36	34
L.J.	3	0	0	0	40	92.7	33	29
E.P.	0	0	0	0	24	65.3	24	28
*M*s for control subjects (n = 8)	20.6	6.0	7.6	8.9	71.3	97.7	41.1	38.1

Note. The diagram recall score is based on the delayed (12-min) reproduction of the Rey–Osterrieth figure (Osterrieth, 1944; maximum score = 36). For copying the figure, the AMN group and Patient E.P. obtained normal scores (29.6 and 27, respectively; Kritchevsky et al., 1988). The paired associates score is the number of word pairs recalled on three successive trials (maximum score = 10 per trial). The word recall score is the mean percentage of 15 words recalled across five successive study–test trials (Rey, 1964). The word recognition score is the mean percentage of words identified correctly across five successive study–test trials (yes–no recognition of 15 new words and 15 old words). Note that scores on the recall test are above zero because on this test of immediate recall, several items can be retrieved from immediate memory, which is intact in amnesia. Note too that recognition scores are above chance, also presumably because some items can be retrieved from immediate memory (E.P.'s score was not reliably above chance, $t[29] = 1.9, p = .07$). The scores for words and faces are based on a 24-hr recognition test of 50 words and 50 faces (modified from Warrington, 1984); maximum score = 50, chance = 25. The mean scores for the control subjects are from Squire and Shimamura (1986).

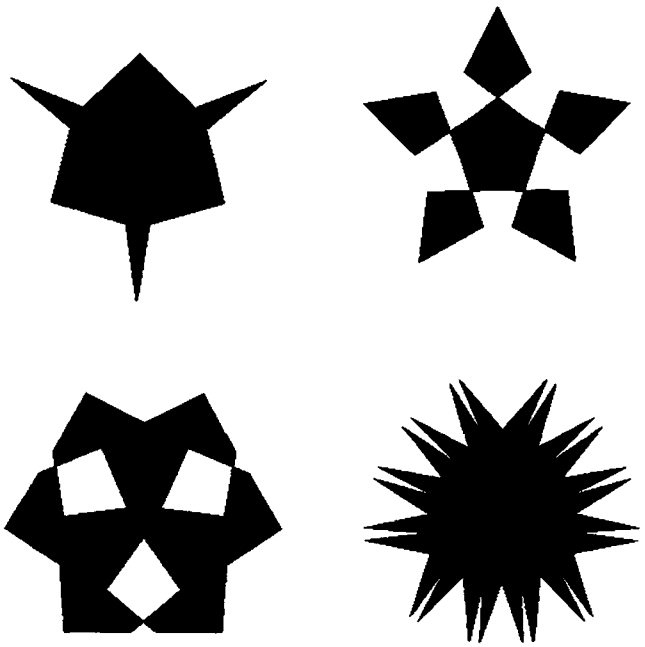

Figure 1. Four examples of the geometric shapes used for the transverse patterning and control problems.

needed to make each response. When a correct shape was chosen, the word *Yes* appeared on the correct shape, a tone sounded for 0.5 s, and the computer screen went blank 2 s after the response. When an incorrect shape was chosen, no feedback was provided, and the computer screen also went blank 2 s after the response. The next trial then began after a 1-s interval. The transverse patterning problem consisted of three phases separated by 30-s breaks, and the two control problems each consisted of only one phase each. In each phase, testing continued until a participant either met a criterion of 14 correct choices out of 15 responses or completed 180 trials.

Transverse patterning problem. The transverse patterning problem, which consisted of three phases, was adapted from Rickard & Grafman (1998). In Phase I, all trials involved the presentation of A+B− (i.e., shape A was correct and shape B was incorrect). In Phase II, half of the trials were the same as in Phase I; the other half involved the presentation of B+C−. The order of the A+B− trials and B+C− trials was random, but no more than two trials of one type occurred consecutively. In Phase III, two thirds of the trials were the same as in Phase II, and the others involved the presentation of C+A−. In Phase III, each of the three trial types occurred once in every group of three trials. In all three phases, the correct shape appeared on the left-hand side of the screen half of the time and on the right-hand side half of the time.

Control problems. Two concurrent pair learning tasks were used as the control problems. The three-pair concurrent learning problem was used because it required participants to learn the same number of pairwise discriminations as did Phase III of the transverse patterning problem (c.f. Rickard & Grafman, 1998). For this problem, each group of three trials involved a randomly ordered presentation of the pairs D+E−, F+G−, and H+I−. The six-pair concurrent learning problem was used because pilot data from other controls indicated that it was about as difficult to solve as Phase III of the transverse patterning problem. For the six-pair problem, each group of six trials involved a randomly ordered presentation of the pairs J+K−, L+M−, N+O−, P+Q−, R+S−, and T+U−. For both problems, the correct shape appeared on the left-hand side of the screen half of the time and on the right-hand side half of the time.

Results

For each phase of the transverse patterning problem and the two control problems, the number of trials that preceded a run of 14 correct choices out of 15 responses was used as the score (trials to criterion). Figure 2 (left panel) shows the number of trials required to meet criterion for each phase of the transverse patterning problem. The CON group required 0.2, 4.3, and 14.0 trials to meet criterion in Phases I, II, and III, respectively. The AMN group easily met criterion in Phase I (zero trials for each patient) but had difficulty meeting criterion in Phases II and III, on average requiring 53 and 104 trials to solve Phases II and III, respectively. Thus, although all 3 patients were able to solve each phase of the transverse patterning problem, they were impaired in Phase II, $t(10) = 6.38$, $p < .001$, and in Phase III, $t(10) = 5.52$, $p < .001$. Finally, E.P. met criterion in Phase I in zero trials but was unable to solve Phases II and III within the 180-trial limit. Presumably, he could solve Phase I by holding the correct answer in mind (in working memory).

Figure 2 (right panel) shows the number of trials required to meet criterion for the two control problems. The CON group met criterion in an average of 3.7 trials on the three-pair concurrent learning problem and in an average of 14.4 trials on the six-pair concurrent learning problem. Thus, controls completed the three-pair problem (3.7 trials) about as quickly as they completed Phase II of the transverse patterning problem (4.3 trials), $t(8) = 0.26$. In addition, they completed the six-pair problem (14.4 trials) about as quickly as they completed Phase III of the transverse patterning problem (14.0 trials), $t(8) = 0.06$.

In contrast to the CON group, the AMN group was impaired at learning both the three-pair problem, $M = 49.3$ trials, $t(10) = 2.97$, $p < .02$, and the six-pair problem, $M = 105.7$ trials, $t(10) = 4.05$, $p < .003$. The AMN group was impaired but exhibited the same pattern of behavior as the CON group. Like the CON group, the AMN group found the three-pair problem ($M = 49.3$ trials) about as difficult as Phase II of the transverse patterning problem ($M = 53.0$ trials), $t(2) = 0.24$. They also found the six-pair problem ($M = 105.7$ trials) about as difficult as Phase III of the transverse patterning problem ($M = 104.0$ trials), $t(2) = 0.04$. Finally, Patient E.P. did not solve Phases II and III of the transverse patterning problem or the three-pair problem within the 180-trial limit.

Overall, the data indicate that the AMN group demonstrated a general learning impairment. This impairment was related to the difficulty of each problem rather than being uniquely associated with the transverse patterning problem itself.

Discussion

Patients with damage limited to the hippocampal formation were impaired at solving a problem requiring a config-

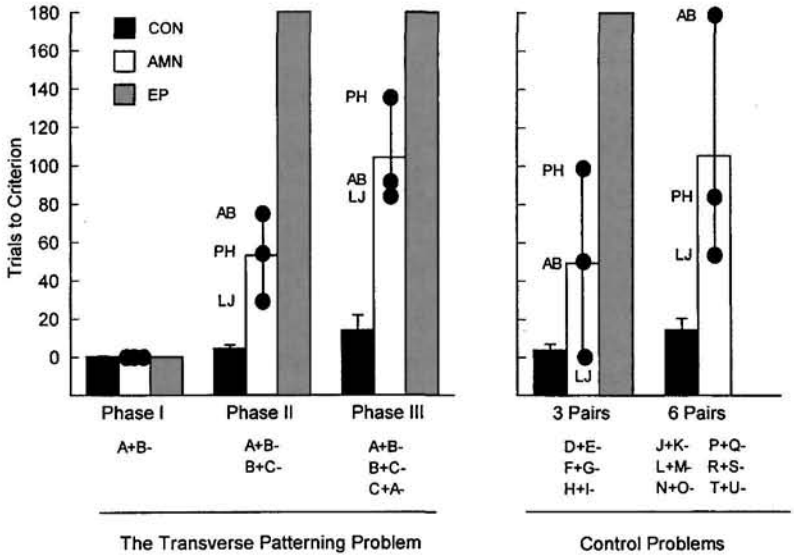

Figure 2. Number of trials required to learn the three phases of the transverse patterning problem (left panel) and the two control problems (right panel). Error bars indicate the standard error of the mean for the control subjects. Individual scores for the amnesic patients are indicated by filled circles labeled with each patient's initials. The maximum possible score for each phase of the transverse patterning problem and for each control problem was 180 trials. CON = 9 controls; AMN = 3 amnesic patients; EP = amnesic patient E.P.

ural solution (i.e., the transverse patterning problem). They were also impaired at solving the two control problems that required only the learning of elemental associations (i.e., the three-pair and six-pair concurrent learning problems). In addition, the six-pair concurrent problem, which was about as difficult for controls as Phase III of the transverse patterning problem, was also about as difficult for the amnesic patients as Phase III of the transverse patterning problem. Finally, the severely amnesic patient E.P. was able to solve neither the transverse patterning problem nor the three-pair concurrent learning problem within the limits of testing.

One earlier study examined the ability of amnesic patients to solve the transverse patterning problem (Rickard & Grafman, 1998). Four amnesic patients with presumed damage to the hippocampal formation and four controls were tested on two different problems: a transverse patterning problem that consisted of three discrimination problems and a control problem that could be solved by learning three elemental associations. The amnesic patients could solve the control problem but could not solve the transverse patterning problem. However, the three-pair problem that was used as a control task (Phase I, A+B−; Phase II, A+B− and C+D−; Phase III, A+B−, C+D−, and E+F−) was not as difficult as Phase III of the transverse patterning problem (a mean of 0 and 13.3 trials were required for 4 controls to learn Phase III of the control problem and Phase III of the transverse patterning problem, respectively). In contrast, in the present study, controls found the transverse patterning problem and the six-pair concurrent learning control problem about equally difficult (Phase III of the transverse patterning problem: $M = 14.0$ trials to learn; 6-pair control problem: $M = 14.4$ trials to learn). Thus, when problem difficulty was unconfounded with problem type (configural vs. elemental), we found no evidence that amnesic patients were selectively impaired on the configural problem.

Our results are consistent with previous findings in experimental animals that hippocampal lesions impair learning of the transverse patterning problem (Alvarado & Rudy, 1995a, 1995b; Alvarado et al., 1995; Dusek & Eichenbaum, 1998) as well as other problems that require the formation of configural associations (Sutherland & McDonald, 1990; Sutherland, McDonald, Hill, & Rudy, 1989; Whishaw & Tomie, 1991). However, the amnesic patients we tested were impaired at solving both the transverse patterning problem and the elemental control problems. If the transverse patterning problem uniquely engages a configural learning strategy and the elemental control tasks do not, then the present findings show that the configural theory does not provide a correct account of hippocampal function.

A potential ambiguity in configural theory concerns the nature of the configuration that is thought to be established during learning. One possibility is that the configuration established during learning is a new compound stimulus that is composed of the elements from the task but does not retain separate information about each task element. In this case, the task has been reduced to the problem of learning about single cues, and rats with hippocampal lesions can learn about single cues by engaging their intact habit system. This

way of describing configural learning does not provide a correct account of hippocampal function.

Alternatively, if the configuration is a constellation of stimulus elements that permits comparisons among the elements and the learning of relationships among the elements, then the idea that the hippocampal formation is needed for configural learning is quite similar to the idea that it is needed for relational (or declarative) learning. In this case, we suggest that the original descriptions of declarative memory as a way to understand amnesia and medial temporal lobe function (Cohen, 1984; Cohen & Squire, 1980; Squire, 1982), the extension of these ideas to relational memory in experimental animals (Cohen & Eichenbaum, 1993; Eichenbaum, 1997), and configural theory (Sutherland & Rudy, 1989) are congruent accounts of hippocampal function.

It appears to us that there are two reasons why it has been difficult to reach agreement about configural learning and hippocampal function. First, species differ in what strategy they adopt in approaching the two-choice discrimination problem. Rodents readily engage a habit strategy in two-choice discrimination tasks and therefore can often solve such tasks successfully despite hippocampal damage. In contrast, humans adopt a declarative strategy for almost all two-choice discrimination problems. Second, within a species, task parameters can determine how the transverse patterning task will be solved. Rodents with hippocampal lesions succeed at the transverse patterning problem if they can approach each unique trial (AB, BA, BC, CB, AC, and CA) as if the trial provided a separate and distinct stimulus. However, rodents fail transverse patterning tasks if they must evaluate each stimulus separately and in relation to the other two stimuli in the task. For cases where rodents with hippocampal system damage likely succeeded at discrimination tasks by treating the whole stimulus compound as a unique cue, see Eichenbaum, Mathews, and Cohen (1989) and Bussey et al. (1998). It will always be useful to apply independent criteria that can determine what strategy an animal has in fact used to solve a discrimination task (for an example, see Eichenbaum et al. 1989).

With these points in mind, the present findings are best understood as an additional demonstration of the importance of the human hippocampal formation for two-choice discrimination tasks. Furthermore, for humans, the transverse patterning problem is simply a set of three concurrent discrimination problems that are difficult to memorize because they contain overlapping elements that cause interference. The transverse pattering task is about as difficult as a set of six concurrent discrimination problems that contain no overlapping elements.

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