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Two functional components of the hippocampal memory system

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Abstract: There is considerable evidence that the hippocampal system contributes both to (1) the temporary maintenance of memories and to (2) the processing of a particular type of memory representation. The findings on amnesia suggest that these two distinguishing features of hippocampal memory processing are orthogonal. Together with anatomical and physiological data, the neuropsychological findings support a model of cortico-hippocampal interactions in which the temporal and representational properties of hippocampal memory processing are mediated separately. We propose that neocortical association areas maintain short-term memories for specific items and events prior to hippocampal processing as well as providing the final repositories of long-term memory. The parahippocampal region supports intermediate-term storage of individual items, and the hippocampal formation itself mediates an organization of memories according to relevant relationships among items. Hippocampal-cortical interactions produce (i) strong and persistent memories for events, including their constituent elements and the relationships among them, and (ii) a capacity to express memories flexibly across a wide range of circumstances.

Keywords: amnesia; entorhinal cortex; hippocampus; learning; memory; parahippocampal region; representation

It has been known for decades that the hippocampal system plays a prominent role in learning and memory. Only recently has it become clear that only certain properties of memory processing depend on hippocampal system function and that these can be distinguished operationally from other aspects of memory that do not. It has proved difficult, however, to arrive at an understanding of memory rich enough to characterize both the nature of memory that is dependent on the hippocampal system and memory that is independent of this processing, and to tie them to underlying neural mechanisms. The earliest reports of amnesia emphasized the time-limited role of the hippocampal region in memory, focusing on its critical function in "consolidation" processes that bridge between immediate memory and the long-term store (Scoville & Milner 1957). This *temporal distinction* is most striking: amnesic patients and animals with hippocampal system damage show normal retention at short delays and increasingly impaired retention with longer delays. Recently, some have argued that virtually all aspects of memory processing by the hippocampal system can be attributed to its function as a temporary memory store or buffer (e.g., Rawlins 1985). However, a large body of data indicates that the loss of consolidation or memory-buffer functions cannot account for the full pattern of impaired and spared memory performance observed after hippocampal system damage; some memory capacities are intact in amnesia even across very long temporal intervals, whereas other aspects of memory performance are grossly impaired even over relatively short retention intervals. The buffer hypothesis also fails to account fully for a number of relevant observations on the stable, long-lasting functional correlates of hippocampal neuronal activity (see sect. 5). To accommodate a broader range of findings, many investigators have proposed a further distinction of hippocampal system function. It has been argued that the hippocampal system plays a role in only one "type" of memory, only one form of memory representation; understanding the nature of this *representational distinction* of memory processing by the hippocampal system has become a dominant theme in contemporary memory research. Progress has been made in characterizing the kind of memory representation impaired in human amnesia and the kind of memory representation deficient in animals with experimental damage to the hippocampal system. Although there continues to be some disagreement about the scope of the deficit and the terminology used to describe it, most investigators agree that there are multiple memory systems with different representational characteristics and that the hippocampal system is critical to only one such system. Our view is that the hippocampal system is involved in *de-*

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clarative memory but not *procedural memory.* We will accordingly adopt a terminology in this target article that distinguishes between (1) a hippocampal system-dependent capacity for *relational representation,* supporting both memory for relationships among perceptually distinct items and flexible expression of memories in novel contexts, and (2) a hippocampal system-independent capacity for *individual representations,* involving the acquisition of biases and adaptations to individual items expressible only through repetition of the learning event (see sect. 4.1).

There has as yet been little research exploring the potential relationships between the temporal and representational distinctions of hippocampal-dependent memory processing. Most investigators, ourselves included, have assumed that the time-dependent properties of hippocampal function are merely a qualification or restriction of the role of this system in a particular type of memory representation. Findings derived from a number of behavioral paradigms, however, are more clearly related to the temporal properties than to the representational ones, suggesting that the temporal properties of hippocampal memory processing are *not* subsidiary to the representational properties.

This target article considers hippocampal memory processing in terms of two orthogonal properties, one involving the strength and persistence of storage within the hippocampal system and another involving the form of memory representation this system supports. It will be argued that (1) hippocampal system-dependent memory differs from hippocampal system-independent memory with regard to both these properties, that (2) specific findings on impaired and spared memory performance in amnesia associated with hippocampal system damage are a consequence of one or the other of these two distinguishing properties, and that (3) these two properties are mediated by different anatomical components of the hippocampal system. We will further argue that the combined temporal and representational properties of the hippocampal system comprise the fundamental characteristics of *declarative memory* in humans and animals.

In the following sections we describe the flow of information in the hippocampal system, proposing specific anatomical assignments for those aspects of hippocampal memory processing responsible for the temporal and representational distinctions described above. In section 1, we describe the scope of this presentation and some anatomical designations critical to our model. In section 2, we sketch the model briefly to introduce the conceptual issues and make empirical predictions. In the third and fourth sections, we further characterize and discuss the empirical basis of the temporal and representational distinctions of hippocampal function in relation to work on human amnesia and on animal models of amnesia (emphasizing particularly the animal work); these sections also outline the evidence that these functions can be dissociated by selective lesions within the hippocampal system. In section 5, we provide converging evidence on the coding properties of neurons in the cortex and hippocampal system of animals performing memory tasks. Section 6 combines the neuropsychological and neurophysiological data in a more detailed description of the model, explicating more fully our view of how these properties contribute to and interact in declarative memory. The seventh and final section compares our model with other theoretical accounts of hippocampal function and, in doing so, demonstrates how the properties of the model draw together central features of these proposals into a more comprehensive account.

1. Some preliminaries

Before addressing the central issues, we will discuss the scope of our account and the anatomical conventions it adopts.

1.1. Limiting the scope of the present account

The aim of this article is to present and support a hypothesis about the distinct and interactive memory functions of the hippocampal system. To keep the focus on this topic, some issues will not be comprehensively reviewed. We will not consider the large body of literature on the effects of hippocampal system damage on behaviors that are only indirectly related to learning and memory, including studies on orientation, distraction, exploration, motor patterns, operant schedules, emotion, and species-specific behaviors (for detailed reviews see Gray 1982; Gray & McNaughton 1983; O'Keefe & Nadel 1978). In making this restriction, we are assuming that changes in these behaviors after hippocampal system damage are either a consequence of amnesia or an indirect result of disconnections of the limbic system that have nonmnemonic as well as mnemonic effects (for further discussion, see Gray & Rawlins 1986).

Nor will our review of the effects of hippocampal system damage on learning and memory be exhaustive. We will focus on the literature that is particularly relevant to contrasting temporal and representational distinctions, and how these properties relate to components of the hippocampal system. We will *not* provide a comprehensive review of studies on human declarative memory, human amnesia, or animal learning and behavior that are not directly relevant to these two distinctions. Our review will accordingly emphasize the animal literature, where selective damage and recording studies can be conducted; the human literature will be surveyed only to show how this work generated the initial observations about the temporal and representational distinctions. Even our coverage of the animal literature will have to be selective, considering carefully a set of behavioral paradigms that are particularly illuminating with regard to the temporal and representational properties of hippocampal function. A more extensive survey of the literature with a full analysis of relational representation in human declarative memory and amnesia can be found in Cohen and Eichenbaum (1993).

1.2. Delineating the anatomical components of the hippocampal system

Since there is no universal agreement on what constitutes the term "hippocampal system," we will describe how we use this term here, justifying the selective inclusion of specific brain structures within what we will argue are the functional components of the system. The term "hippocampal region" was first used to describe the set of medial

temporal lobe structures removed in the patient H.M., whose resulting amnesia has been the subject of neuropsychological study for nearly 40 years (see below). In his case, the surgical removal included most of the hippocampus (Ammon's horn), the dentate gyrus, the subicular complex, the amygdala, and perhaps parts of several cortical structures including the entorhinal, perirhinal, and piriform cortices (Scoville & Milner 1957). Comparisons of H.M.'s memory performance with that of patients who have had more restricted medial temporal lobe removals indicated that the degree of damage to the hippocampus *per se* determined the severity of amnesia; consequently, much memory research has focused on this particular structure. Subsequent efforts to model the amnesic syndrome in animals by selectively ablating the hippocampus were disappointing, however; monkeys and rats with hippocampal lesions were not severely impaired at many common discrimination learning tasks used in memory research in animals.

A breakthrough came when Mishkin (1978) reported that monkeys with conjoint but not separate damage to the hippocampus and amygdala were severely impaired in recognition memory for objects, suggesting that a medial temporal lobe removal as complete as H.M.'s was necessary and sufficient to produce severe global amnesia in animals. More recent experiments, however, have modified this conclusion in two ways. First, it is now clear that restricted amygdala lesions do not cause impairment on tasks sensitive to large medial temporal damage, and they do not exacerbate the memory deficit resulting from damage to other medial temporal structures (Zola-Morgan et al. 1989a). These findings have redirected attention to the damage caused in cortical areas adjacent to the hippocampus that inevitably occurs during surgical removal of the amygdala or hippocampus. Second, it has recently been demonstrated that substantial damage to the surrounding cortical areas alone produces as great a deficit in certain task performances as does removal of the entire medial temporal lobe, indicating that these areas play a direct and critical role in memory processing (Murray & Mishkin 1986; Zola-Morgan et al. 1989c; for review see Squire & Zola-Morgan 1991).

Based on the current state of the neuropsychological findings, we conclude that the critical structures comprising the medial temporal memory system include the hippocampus proper (Ammon's horn), the dentate gyrus, the subicular complex, and surrounding cortical areas including the entorhinal, perirhinal, and parahippocampal areas. Furthermore, for purposes that will become apparent, we have adopted a terminology consistent with that suggested by Witter and colleagues (1989), distinguishing the *hippocampal formation* and the *parahippocampal region* as the two major functional components of the *hippocampal system.* In the following discussion we will include within the hippocampal formation Ammon's horn, the dentate gyrus, the subiculum, and the fornix; and within the parahippocampal region the entorhinal, perirhinal, and parahippocampal cortices. [Note: "parahippocampal cortex," a discrete area in the primate cortex, is not to be confused with the "parahippocampal region," which includes this specific cortical area plus the entorhinal and perirhinal cortices.] Figure 1 is a schematic diagram indicating the functions associated with these areas and the flow of information between them and

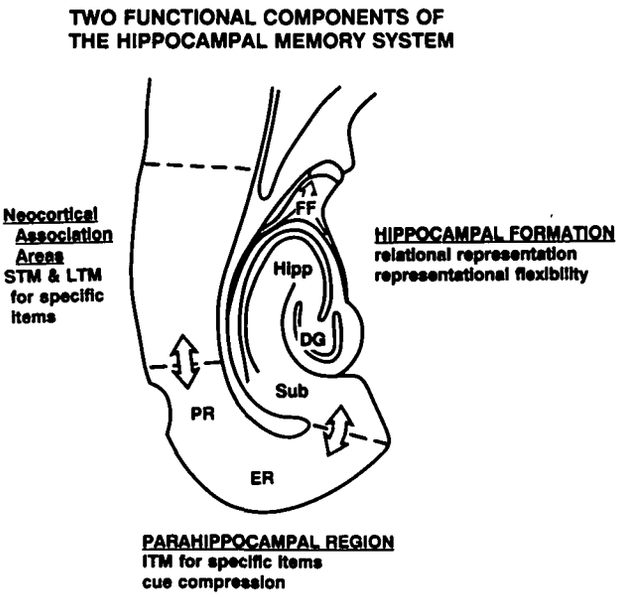

Figure 1. A schematic diagram of components of the hippocampal system, their connections with neocortical association areas, and their putative memory-processing functions.

the neocortex. In this summary we introduce the basic anatomical associations between the neocortical areas that provide specific perceptual and motor information to the hippocampal system, the parahippocampal region, which serves as a convergence center for neocortical inputs and mediates two-way communication between cortical association areas and hippocampal processing, and the hippocampal formation itself (Amaral & Witter 1989; Deacon et al. 1983; Van Hoesen et al. 1972).

Before discussing in detail the functional assignments proposed for these areas, it is important to justify this particular anatomical segregation of functional units in the hippocampal system. With regard to the hippocampal formation, each of the subdivisions of this area is well defined and largely comparable in the monkey and rat (Figure 1; cf. Rosene & Van Hoesen 1987). Our conclusion that the subiculum should be included is supported by both neuropsychological and anatomical findings. The most relevant neuropsychological evidence comes from the elegant experiments in which Jarrard and colleagues made selective neurotoxic lesions in particular subdivisions of the hippocampal formation (see Jarrard 1986; 1993). Results from these studies consistently indicate that ablation of all of these components is critical to producing severe memory impairment in spatial and nonspatial tasks (Jarrard 1986). Jarrard has interpreted his findings as indicating a preferential role for Ammon's horn and the dentate gyrus in spatial learning. This conclusion was based largely on the finding that damage to Ammon's horn and the dentate gyrus are sufficient to produce spatial memory deficits and that subicular damage must be included to produce a deficit in nonspatial memory. More recent work, however, using the sensitive test of the Morris water maze, indicates that even in spatial learning a severe deficit is found only after combined damage to the subiculum as well as Ammon's horn and the dentate gyrus (Morris et al. 1990). Thus, based on the current state of the findings, it appears that the most restricted hippocampal system lesion that produces maximal im-

pairment in any task must include the combination of structures that comprise the hippocampal formation. With regard to anatomical evidence, consistent with the behavioral data, Amaral and Witter (1989) and Witter (1989) viewed the subiculum as the final stage of intrinsic processing in the connectional "loops" between the parahippocampal and hippocampal areas. Their reviews of hippocampal pathways placed the subiculum as the fourth and final stage of serial hippocampal processing through the so-called trisynaptic circuit and drew close parallels between the parahippocampal connections with Ammon's horn and with the subiculum.

In addition, it is important to consider at the outset a designation for the fornix, the major fiber bundle that connects all subdivisions of the hippocampal formation with the septum and other subcortical areas. A complete transection of the fornix disrupts cholinergic and GABAergic function and electrical activity and induces morphological reorganization in the hippocampal formation (e.g. Lahtinen et al. 1993). Thus, a fornix transection produces significant disruption of information processing and output of the hippocampal formation, and so would be expected to have the same functional consequences as damage to the hippocampal formation itself. Notably, a fornix transection does not disconnect the parahippocampal region from the neocortex. A fornix transection may not disrupt functions that can be carried out by the parahippocampal region independent of processing by the hippocampal formation, and hence would not be expected to produce the full-blown amnesia seen following more complete hippocampal system damage. Combining these behavioral and anatomical observations, we will hereafter consider the subiculum and fornix, along with Ammon's horn and the dentate gyrus, as critical elements of a functional unit within the hippocampal system.

With regard to the parahippocampal region, all three cortical areas that we include in this region are well defined in the monkey, but less so in the rat (Amaral et al. 1987; Deacon et al. 1983; Witter et al. 1989). In both species the entorhinal cortex has been characterized as a cytoarchitecturally distinct area surrounding the hippocampal formation and contributing the major cortical afferents to the hippocampal formation. It is a heterogeneous area composed of several subdivisions with topographically contiguous and often overlapping projections into the hippocampal formation (see Amaral & Witter 1989). The perirhinal cortex, composed of Brodmann's areas 35 and 36 bordering the rhinal sulcus, is also distinguishable in both the rat and monkey, although the extent of its borders in the rat are not fully clear. The parahippocampal cortex in the monkey is clearly distinguished as the combination of von Bonin and Bailey's areas TH and TF lying posterior to the perirhinal cortex. There is no general agreement as to whether the same area exists in rats, but connectional correspondences have led Deacon et al. (1983) to propose that the "postrhinal" cortex that forms the caudal continuation of the rhinal sulcus is homologous to the primate parahippocampal cortex. In addition to these cytoarchitectural distinctions, the subdivisions of the parahippocampal region are distinguished from each other by several connectional differences. For example, in the monkey, the perirhinal area receives the greater input from higher visual areas while the parahippocampal cortex receives the greater input from the parietal and cingulate cortices (Suzuki & Amaral 1993; 1994); a similar topography of inputs distinguishes the perirhinal and postrhinal areas of the rat (Deacon et al. 1983). A major similarity of the perirhinal and parahippocampal (postrhinal) areas is that both heavily project to parts of the entorhinal cortex. Despite the various differences in the cytoarchitecture and extrinsic connections of the entorhinal, perirhinal, and parahippocampal cortices, these areas can be characterized as receiving input from multiple neocortical association areas and thus comprise an important convergence site for neocortical input to the hippocampus (Deacon et al. 1983; Squire et al. 1989; Witter et al. 1989). Furthermore, each is reciprocally connected with both neocortical areas and with the hippocampal formation, thus serving as the major intermediary in communication between the hippocampal formation and neocortex. The precise pattern of cortical and hippocampal connections differs among these structures, but the neuropsychological data have not yet revealed any corresponding functional distinctions (see below and Witter et al. 1989). Given these commonalities, we will refer to these areas collectively as a functional unit at the risk of overshadowing potentially important functional distinctions that may yet be discovered.

In addition, there is some controversy about the limits of the cortical areas that should be included within the parahippocampal region, particularly as related to visual memory in primates. In primates, just adjacent to the parahippocampal region is a portion of the inferotemporal cortex (anterior inferotemporal cortex or TE1), an area critically involved in higher order visual identification and memory (Gross 1973). As will be discussed below, some of the memory-processing properties of cells in this area are very similar to the features of cells in the parahippocampal region, suggesting that at least part of this area may be more reasonably considered an adjunct to the parahippocampal region, with its role limited to visual memory processing.

Finally, we should acknowledge that there is a danger of circularity in defining the hippocampal system based on neuropsychological findings because, as will become clear in the following discussion, a precise characterization of the memory processes supported by this system is itself still evolving. Thus, the operational definition of "the hippocampal system" may change as we refine the characterization of memory deficits resulting from circumscribed damage to particular structures. For the moment, however, we interpret the converging anatomical, behavioral, and electrophysiological evidence as suggesting particular temporal and representational functionalities mediated differentially within separate components of the hippocampal system.

2. The role of the hippocampal system in intermediate-term storage and relational representation: A model of successive stages in hippocampal mediation of declarative memory

Below we propose a model that attributes to the hippocampal system two sequential functions corresponding to anatomically separate components of this system. First,

the hippocampal system has the capacity to represent isolated (nonrelational) items at full strength and to hold these representations in a memory "buffer" for periods of at least several minutes; the persistence of these representations may depend on the nature of the stimulus material and can be extended considerably by repetition (see discussion in sect. 3.2). Intermediate-term memory is thus defined here as bridging the gap between the very brief span of immediate (or short-term) memory and the potentially permanent (or long-term) memory store. Like permanent memory, and unlike immediate memory, the intermediate-term store is viewed as sustaining retention across some interfering or distracting event but, unlike permanent memory, this form of representation cannot be sustained indefinitely. Second, during this intermediate period, the hippocampal system subserves processing that involves comparing and relating these individual representations to other memory representations, creating relational representations according to the relevant contingencies between the items and the structure of any already established memory organization that involves those items. The combination of these two processing functions comprises *declarative memory* as we have characterized it.

According to this account, although these two processing functions are supported independently, they normally function interactively, with the relational memory processes operating on an intermediate-term store of new items. Thus the temporal and representational properties of the hippocampal system are considered partially interdependent; relational memory processes depend on the intermediate-term store, but intermediate-term storage of single items does not require relational memory processing. This hypothesis is most simply instantiated by a two-stage model in which the intermediate storage function is accomplished at an earlier stage of the hippocampal system than relational processing. In this target article we propose that just such a functional distinction exists; specifically, that intermediate-term storage of individual representations is supported primarily by the parahippocampal region and that the hippocampal formation mediates relational processing (see Fig. 1). These two subdivisions will be distinguished from the closely related neocortical association areas that are reciprocally connected with the hippocampal system and, as will be argued below, contribute to memory processing in different ways.

Our proposal regarding the functional roles of the hippocampal formation and the parahippocampal region generates two sets of testable predictions. First, the present account predicts that damage to the parahippocampal region should result in a loss of intermediate-term storage capacity for individual items; this damage should also inevitably result in a deficit in relational processing consistent with the view that intermediate-term storage is a prerequisite for a relational memory representation. By contrast, damage to the hippocampal formation or its noncortical connections via the fornix should selectively affect relational memory processing, leaving intact a capacity for intermediate-term storage of nonrelational information. Further supporting evidence might be obtained through observations on the behavioral physiology of the hippocampal system and the neocortical structures that are the source of much of the information this system receives. The model predicts that neural activity within the parahippocampal region should reflect intermediate-term storage for specific and isolated items and events, whereas activity in the hippocampal formation should be strongly associated with relations among those items. To our knowledge no existing experiments explicitly intended to test these predictions. Nevertheless, there exists a large body of data on the behavioral effects of damage to the hippocampal system, including several studies involving selective damage restricted to either the parahippocampal region or the hippocampal formation; many of these studies assess the effects of these lesions on performance that depends upon intermediate-term storage or relational representation. In addition, there have been a number of recent examinations of the behavioral physiology of both the cortical association areas and the hippocampal system in animals performing recognition memory and other learning tasks. In the following sections we will summarize some of the relevant findings, showing how they support predictions of the theoretical claims that were outlined above and that will be explicated more fully below.

3. Temporal properties of hippocampal system-dependent and hippocampal system-independent memory

In 1953 the patient H.M., who had for years suffered frequent major epileptic seizures that were uncontrollable by pharmacological treatment, was operated on and the medial temporal lobe area, including the hippocampus and neighboring structures, was removed (Scoville & Milner 1957). Subsequent to this surgery, H.M. demonstrated a profound deficit in new learning that apparently extended to all types of materials, leading to the characterization of his impairment as "global" anterograde amnesia. However, from the very first reports it has been clear that the range of this amnesia was distinguished by its restricted temporal domain. H.M. was almost totally unable to retain new information for extended periods, although he demonstrated an intact immediate or short-term memory capacity. In addition, much of his remote memory was intact, exemplified by his retention of language skills, general world knowledge, and childhood memories. Despite the preservation of remotely acquired information, memories H.M. acquired nearer to the time of his operation were lost; his retrograde amnesia extends 3–11 years before his surgery (Corkin 1984). Contrasting H.M.'s deficit in new learning with his intact short-term and remote memory capacities suggested that the amnesia associated with hippocampal system damage could be viewed as an impairment in the encoding, maintenance, or "consolidation" of enduring and accessible memories. The same pattern of temporally dependent impairment and sparing of memory has since been described in several other patients with medial temporal lobe damage (see Squire 1987).

3.1. Animal models of hippocampal involvement in intermediate-term memory

A considerable number of studies, using a variety of learning paradigms, have demonstrated both delay-

dependent impairment in new learning (Aggleton et al. 1989; Alvarez-Royo et al. 1992; Gaffan 1974; Kesner & Novak 1982; Mishkin 1978; Otto & Eichenbaum 1992a; Overman et al. 1990; Staubli et al. 1984; 1986; Zola-Morgan & Squire 1985) and temporally graded retrograde amnesia (Kim & Fanselow 1992; Winocur 1985; 1990; Zola-Morgan & Squire 1990) in animals with hippocampal system damage. These findings make it clear that the hippocampal system is neither a critical site for short-term memory nor the sole final repository for long-term memory; rather it plays a critical role during the intermediate period that bridges between them. The locus of storage for short-term and permanent memories is not known, but it is widely believed to be in the neocortical areas interconnected with the hippocampal system. Also, whether the hippocampal system actually *stores* memories or mediates some interaction among other (presumably neocortical) storage sites *during* the time after learning, when hippocampal system involvement is necessary, remains unclear. [For further discussion on these points, see sect. 5 and reviews by Eichenbaum et al. (1992b), Halgren (1984), Squire et al. (1984); Teyler & Discenna (1986).]

Recent efforts to delineate the anatomical structures involved in intermediate-term memory maintenance have focused on the delayed nonmatch-to-sample (DNMS) task. Each trial of the DNMS task is composed of three phases. In the first phase a sample memory cue is presented. This is followed by a delay phase during which the memory for that cue must be maintained. Finally, in the choice phase, the subject is presented with the sample and a novel stimulus, and the unfamiliar nonmatch cue must be selected. The load on memory can be increased by lengthening the delay phase or by presenting a list of sample cues prior to a series of choice recognition tests. This paradigm was first developed for monkeys, using three-dimensional junk objects that provide rich and salient cues for this species (Gaffan 1974; Mishkin & Delacour 1975). Stimuli were used only once or very infrequently across trials, thereby eliminating the high level of interitem interference prominent in other related tasks, including delayed match to sample with trial-repeated cues, delayed response, and delayed alternation. Damage to the hippocampal system results in a performance deficit that is dependent on the duration of the delay or the length of the sample list (Gaffan 1974; Mishkin, 1978), revealing a delay-dependent deficit in new learning similar to that observed in human amnesics (e.g., Mishkin 1982). Indeed amnesic patients also demonstrate delay-dependent impairment on versions of DNMS developed for testing human subjects (Aggleton et al. 1988; Squire et al. 1988). Finally, the DNMS paradigm has been revised successfully for testing recognition memory in rats by using visual-tactile or olfactory stimuli as memory cues (Aggleton et al. 1986; Mumby et al. 1990; Otto & Eichenbaum 1992a; Rothblat & Hayes 1987) and, in some of these studies (see below), damage to the hippocampal system results in the same deficit observed in monkeys and humans.

Whereas the DNMS paradigm has been extraordinarily fruitful in studies delineating the components of the hippocampal system necessary for this type of simple recognition memory (see Squire & Zola-Morgan 1991), it is not clear to what extent the cognitive demands of DNMS rely on the representational properties of memory that depend on the hippocampal system. The hippocampal system might participate in this kind of recognition memory by supporting a judgment of the relationship between perceptual information available during the choice phase and memories for experiences with previous stimuli. It may also play an important role in selecting a nonmatch response because nonmatching requires a "flexible" response – that is, a choice contrary to that performed during the sample phase. For both of these reasons, hippocampal processing may confer an advantage to normal subjects. However, given that DNMS is typically run with trial-unique stimuli, memory processing that occurs outside the hippocampal system and is based upon the familiarity of sensory features of individual stimuli might support DNMS performance without representing the relationship between the sample and other previous stimuli, or of the episode surrounding previous experience with a familiar item. Indeed, recent work with human amnesia suggests that "familiarity" or perceptual fluency can provide a basis for some recognition memory judgments (e.g., Verfaillie & Treadwell 1993). It is notable that the nonmatch response requirement of DNMS is not critical to the demonstration of a memory deficit; monkeys with hippocampal system damage are significantly, if not as severely, impaired when the requirement is to match to the sample cue (Gaffan et al. 1984a; 1984b; Mishkin et al. 1984; Rawlins et al. 1988). Most important, in both matching and nonmatching, and across the range of variants on DNMS tasks, the presence and magnitude of impairment after hippocampal damage is primarily determined by the duration of memory delay, or the delay introduced when lists of sample stimuli are used (see, especially, Alvarez-Royo et al. 1992; Overman et al. 1990). These findings suggest that the DNMS task is particularly sensitive to the strength and persistence characteristics of hippocampal memory processing.

The findings on object discrimination learning tasks are relevant and illuminating here because, as with the DNMS task, the performance of animals with hippocampal system damage is best predicted by the duration of memory delay and not by appeal to a representational distinction (cf. Mishkin et al. 1984). Monkeys with hippocampal system damage are mildly impaired in learning simple object discriminations, and more impaired in delayed (48 hour) retention of these discriminations, although these animals can eventually satisfy a criterion of accurate performance (Zola-Morgan & Squire 1985). Furthermore, monkeys with hippocampal system damage perform more poorly when the interval between stimulus repetitions is elongated and the memory load is increased by presenting multiple, concurrent object discrimination problems than when problems are presented one at a time with relatively short repetition intervals (Correll & Scoville 1965a; Moss et al. 1981). A similar pattern of findings is observed in rats with hippocampal system damage – they normally acquire single-pair object discriminations but are impaired in learning the same discriminations presented concurrently (Wible et al. 1992). In addition, Staubli et al. (1984) reported that rats with entorhinal lesions acquired normally simultaneous odor discriminations with massed trials, but were impaired even on single discriminations if trials were spaced by 10 minutes. In considering the representational demands of

object discrimination, a hippocampal coding of relationships between experiences with discriminative stimuli could mediate performance, but differential responding could also be supported by acquisition of biases for individual discriminative stimuli accomplished independent of the hippocampal system. Thus, object discrimination could be supported within or outside of hippocampal representations, and the data on object discrimination seem to fall outside of the representational distinction. Rather, it seems that impairment is observed in monkeys with hippocampal system damage only when the temporal gap that must be bridged is sufficiently long, or when the number of items that must be maintained in memory becomes sufficiently large (Correll & Scoville 1970). As with the pattern of findings on DNMS, it appears that the object discrimination task is primarily sensitive to the strength and persistence characteristics of hippocampal memory processing.

The data so far described are consistent with the view that preserved short-term memory supports both DNMS performance at brief delays and single-pair object discrimination learning with brief intertrial intervals; monkeys with hippocampal system damage are impaired whenever the delay in DNMS or the repetition interval in object discrimination learning is sufficiently long. However, additional data reveal an upper as well as a lower time limit of hippocampal involvement. Thus, unlike with massed training on concurrent object discrimination, monkeys with hippocampal system damage perform as well as normal subjects on a 20-pair concurrent object discrimination if the repetition rate for each problem is very long – that is, when each problem is presented only once per daily training session (Mishkin et al. 1984). This surprising finding indicates that there is an "outside" temporal boundary to memory processing mediated by the hippocampal system. According to this interpretation, monkeys with hippocampal system damage perform as well as normal subjects on 24-hour concurrent discrimination. This is because the hippocampally mediated representation of object memories dissipates in less than one day, making acquisition of this task independent of hippocampal system involvement in normal monkeys as well. Most relevant to the point of this target article is that the representational demands of the conventional concurrent discrimination and the 24-hour delay concurrent discrimination are identical. Thus, the most parsimonious explanation of this pattern of findings is that the hippocampal system subserves a memory store of *intermediate* duration, at least for representations of single isolated stimuli. As will be discussed at length below, the intermediate storage of more complex information, such as spatial arrangements and other examples of relational information, involves the entire hippocampal system.

3.2. Differential contributions of hippocampal system components to intermediate-term memory for single items

The above described observations are based on comparing the performance of normal animals with that of animals with various subtotal or complete removals of the hippocampal system. A review of the data on DNMS in monkeys and rats with damage confined to specific hippocampal system structures indicates that the capacity for intermediate-term storage of single perceptual representations is supported by processing within one particular area of the hippocampal system. These results, summarized in Figure 2, suggest that the parahippocampal region is selectively critical to intermediate-term storage supporting recognition memory in the DNMS task. In monkeys, transection of the fornix, which disconnects the hippocampal formation from subcortical structures, does not affect performance over intermediate retention intervals, although modest impairment is observed at very long delays (Bachevalier et al. 1985; Gaffan et al. 1984a; Zola-Morgan et al. 1989b). Ablation of the hippocampal formation plus partial removal of the parahippocampal region, or cell loss restricted to the hippocampus as a

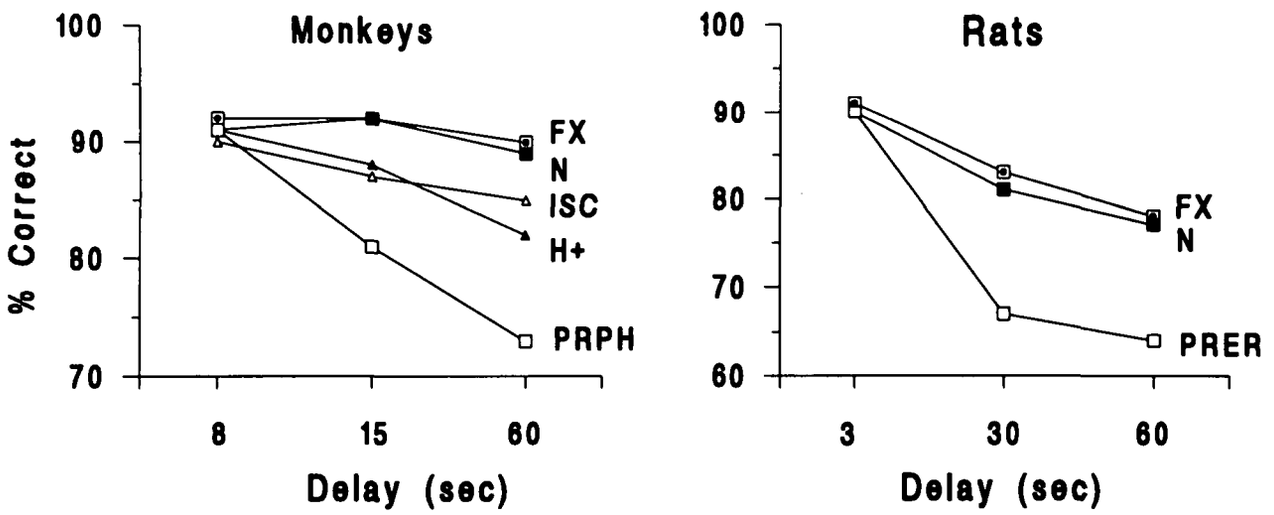

Figure 2. Recognition memory performance in the delayed nonmatch-to-sample (DNMS) task after selective damage to different components of the hippocampal system in monkeys (left) and rats (right). FX = fornix; H+ = hippocampal formation plus partial parahippocampal region damage; ISC = ischemic damage limited primarily to the hippocampus; N = normal or sham operated animals; PRER = perirhinal and parahippocampal cortex; PRPH = perirhinal and parahippocampal cortex. The data shown on the left panel are replotted from Zola-Morgan et al. (1989b; 1989c; 1992). The data on the right panel are replotted from Otto and Eichenbaum (1992a).

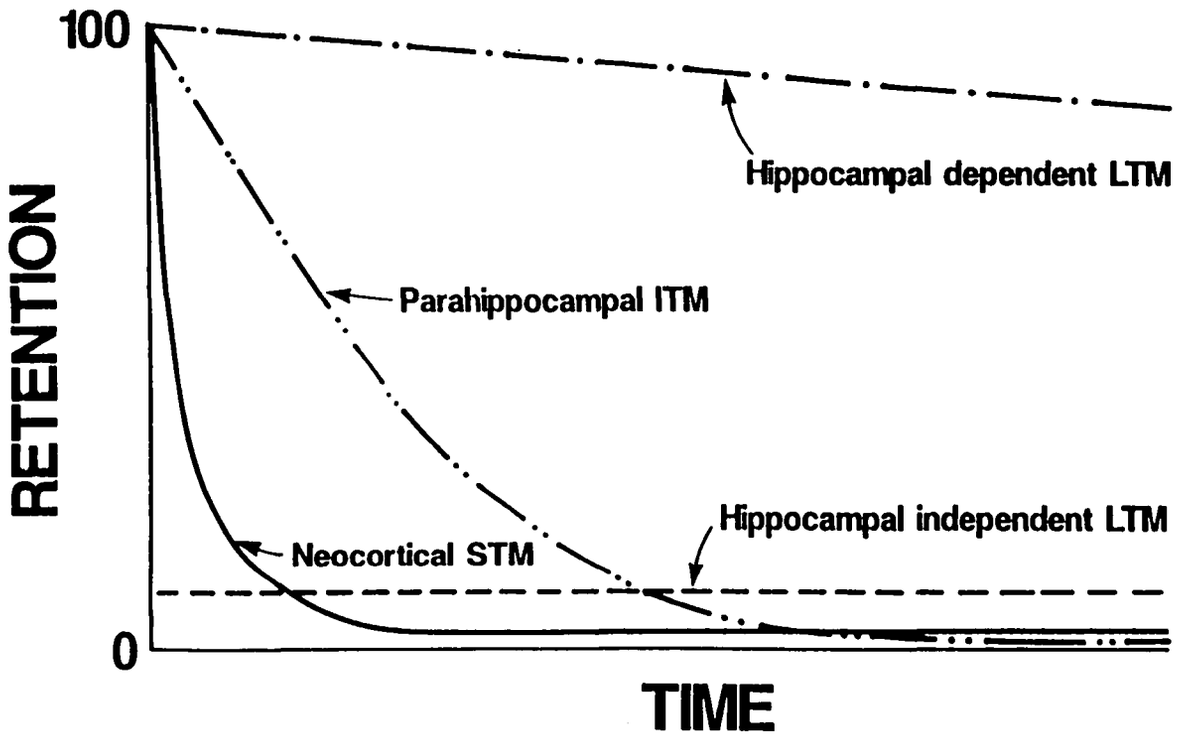

Figure 3. Idealized retention functions for different contributions to recognition memory from a single exposure to an object cue. ITM = intermediate-term memory; LTM = long-term memory; STM = short-term memory.

result of a transient ischemic event, results in modest impairments on DNMS (Zola-Morgan et al. 1989b; Zola-Morgan et al. 1992). By contrast, selective damage to the parahippocampal region, specifically the removal of perirhinal-parahippocampal cortex (Suzuki et al. 1993; Zola-Morgan et al. 1989c) or parts of the perirhinal-parahippocampal and entorhinal areas (Gaffan & Murray 1992; Murray & Mishkin 1986), results in a profound deficit in DNMS performance over intermediate periods – that is, periods beyond a few seconds – with the magnitude of the impairment directly related to the length of the delay. These data clearly indicate that the cortical areas adjacent to the hippocampal formation play a more important role in intermediate-term retention of memories for specific objects than does the hippocampal formation itself (see also Horel 1978). The finding that damage limited to the fornix or hippocampal formation results in a modest deficit suggests that a declarative representation mediated by the hippocampal formation confers only a modest advantage to intact animals.

The findings from experiments on the effects of selective hippocampal system lesions in rats performing DNMS tasks that use trial-unique or infrequently used stimuli are entirely consistent with the data on monkeys (Figure 2, right; see also Rawlins et al. 1991). These experiments have shown that lesions of the hippocampus or fornix produce little or no effect on recognition memory for single, nonrepetitive stimuli over intermediate periods, although deficits have been observed at very long delays (Aggleton et al. 1986; Mumby et al. 1992; Otto & Eichenbaum 1992a; Rothblat & Kromer 1991). By contrast, damage to the perirhinal and entorhinal cortex results in a pattern of delay-dependent impairment in intermediate-term memory that parallels the phenomena in monkeys with the same cortical damage (Otto & Eichenbaum 1992a). Rats with combined hippocampus-amygdala lesions that included some damage to the cortex, but not isolated hippocampal lesions, have demonstrated a similar impairment (Aggleton et al. 1989). Jarrard (1993, p. 15) came to a similar conclusion based on his studies of selective hippocampal and entorhinal lesions in rats. He found that entorhinal lesions, but not hippocampal lesions, resulted in delay-dependent impairment in intermediate-term memory in an object recognition task and impaired acquisition of a concurrent object discrimination. Combining the data for versions of the DNMS task across species, it is clear that the parahippocampal region plays a much larger, if not fully selective, role compared to that of the hippocampal formation in intermediate-term retention of representations for single sensory cues. Although a fully formed representation mediated by the hippocampal formation might confer some advantage to normal animals on DNMS over that of animals *without* normal hippocampal function but with an intact parahippocampal representation, the advantage is relatively small and appears only at very long retention intervals.

Combining the findings across these studies, and anticipating findings from the neurophysiological studies to be discussed below, one can approximate a set of "persistence functions" for distinct brain structures as a way of envisioning how object recognition performance is supported by different components of our model. Figure 3 provides idealized persistence functions generated from a single exposure to an object, compared for the anatomical components of the model. Neocortical areas are seen to support only a short-term trace for such memories, illustrated as a rapidly decaying retention function. The parahippocampal region is seen to add a more persistent representation, one that would support object recogni-

tion for intervals of several minutes. By contrast, hippocampal system-independent pathways support a persistent – hence long-term memory (LTM) – representation of relatively low "retention strength" after a single exposure. The actual performance of intact animals at any particular retention time can be envisioned as the sum of the strengths contributed by the neocortical, parahippocampal, and hippocampal system-independent representations (excluding, for the purposes of this exposition, the contribution of hippocampal system-dependent LTM). By comparison, the performance of animals with damage to the parahippocampal region can be viewed as the sum of the neocortical and hippocampal system-independent representations only (again, excluding hippocampal system-dependent LTM), resulting in a steep delay-dependent performance curve. For a final comparison in this figure, an additional idealized curve is included to indicate the strength of a representation following a stimulus that had been processed sufficiently by the hippocampus itself, permitting the establishment of a robust and potentially permanent memory trace. Such a hippocampal system-dependent LTM representation, although likely to be engendered by significant life events, is improbable following single exposures to cues in the tasks described above. Rather, long-term retention would normally be built up through repetitive exposures.

4. Representational properties of hippocampal system-dependent and hippocampal system-independent memory

Even as the early studies on H.M. and other amnesic patients generally concluded that the memory deficit associated with medial temporal damage extended across all modalities of testing materials, some exceptions were noted – particularly the acquisition of motor skills (Corkin 1968; Milner 1962) and perceptual "priming" tasks (Warrington & Weiskrantz 1968). Over the last 25 years it has become increasingly clear that these "exceptions" were examples of a large range of preserved learning capacities that fit within the same temporal domain associated with impairment on other learning and memory paradigms (see Cohen 1984; Cohen & Eichenbaum 1993; Corkin 1984; Squire 1987; 1992). Thus, for example, amnesic subjects can learn to draw from a mirror image view and to identify pictures from partial information even when repeated presentations are widely spaced, and even when they cannot explicitly recall the learning experience. Other experiments have indicated that learning involving the identical materials may be either substantially impaired or completely spared in amnesic subjects. This depends on whether memory is assessed directly (*explicitly*), by asking subjects to use conscious recollection of the study phase and the materials presented therein, or it is assessed indirectly (*implicitly*), by evaluating changes in actual processing performance caused by exposure to test materials (e.g., Graf et al. 1984).

Substantial consensus has been reached in characterizing the amnesia following hippocampal system damage as a selective impairment in *declarative* (or *explicit*) memory. This is the kind of memory involved in our recall of everyday facts and events. Such memories can be brought to conscious recollection, are typically subject to verbal reflection or other explicit forms of recall, and can be used flexibly in a variety of situations outside that of the learning experience (Cohen 1984; Cohen & Squire 1980; Squire 1987). Nearly all conventional assessments of human recall and recognition require or emphasize the explicit expression of memories, and performance across this wide range of tasks is severely impaired in amnesia associated with hippocampal system dysfunction. By contrast, the domain of preserved learning in amnesia has been described as *procedural* memory, a collection of capacities that can be revealed in the absence of conscious recollection or verbal reflection, and that are expressed implicitly through enhanced or altered performance during the repetition of relevant aspects of the learning experience (Cohen 1984; Cohen & Squire 1980; Schacter 1987). Most of the behavioral paradigms in which procedural memory has been studied involve the acquisition of various perceptual, motor, or cognitive skills, and several forms of adaptation and bias in performance (reviewed in Cohen 1984; Cohen & Eichenbaum 1993; Squire 1992). Perhaps the most studied of these paradigms involves the "priming" phenomenon by which normal subjects are more likely to complete or recognize pictorial or verbal items from familiar partial information, or to read more quickly or name more quickly recently experienced text or pictures of objects. Human amnesics often perform normally on such tasks, although they are unable consciously to recollect their testing experiences. Notably, such enhanced performance in both normal subjects and amnesics is inflexible in that it succeeds only when the physical form of the test item closely matches that of the previously experienced item (e.g., Schacter 1985; Tulving & Schacter 1990).

4.1. Animal models of hippocampal system-dependent memory representation

It became clear very early in the development of animal models of amnesia that in monkeys, rats, and rabbits, circumscribed hippocampal system damage impaired performance in some tasks but spared performance in others. These findings, and many others in both the human and animal literature, support the notion that in animals, as in humans, there are multiple memory systems that participate in permanent memory storage and that the hippocampal system is critical only to a particular type of memory or aspect of memory representation. Several proposals have been developed that attempt to characterize the form of memory representation dependent upon the hippocampal system in animals, with each proposal based on a different set of behavioral data contrasting hippocampal system-dependent and independent forms of learning.

A critical question in this area of research concerns the extent to which the pattern of impaired and spared capacities in human amnesics and animals with hippocampal system damage can be captured in a single characterization. We have proposed (Eichenbaum et al. 1992a; 1992b), as have other investigators (e.g., Squire 1992), that the data on human amnesia and on animals with hippocampal system damage may indeed share a common fundamental basis. Extending the inference from work on human amnesia that declarative memory mediates com-

parisons among items in memory and permits the flexible use of memories in novel situations (Cohen 1984), our account suggests that the hippocampal system mediates the storage of the outcomes of these comparisons in terms of critical relations among items. Such a *relational representation* constitutes a memory "space," an elaborate organization that permits access to memories via novel routes and supports the flexible expression of memories via pathways not previously exercised (Eichenbaum et al. 1992a). In the absence of relational representation one would still expect intact learning that can be acquired through *individual representations* involving the improvement of specific motor routines, adaptations of sensory-motor responses, or the biasing of responses toward specific, isolated items. The central properties of relational and individual representations can be summarized from our comprehensive review (Cohen & Eichenbaum 1993) as follows:

> *Relational representations* . . . are created by and can be used for comparing and contrasting individual items in memory, and weaving new items into the existing organization of memories. This form of representation maintains the "compositionality" of the items, that is, the encoding of items both as perceptually distinct "objects" and as parts of larger scale "scenes" and "events" that capture the relevant relations between them. [They] . . . support the flexible use of memories by permitting access to items from various sources and by permitting the expression of memories in various, even novel, situations.
>
> *Individual representations* . . . involve the "tuning" or biasing of items within separate processing modules of the brain operating in isolation. Depending on the operating characteristics of these modules, individual representations can incorporate combinations of stimulus elements, but such processing involves the fusion of stimulus elements into a single representation lacking the property of compositionality. [They] . . . can support alterations in performance during repetitions of the processing events that occurred during the original learning experience, but are inflexible in that they cannot be accessed or expressed in novel situations.

The above descriptions of relational and individual representation (greatly abbreviated here; see Cohen & Eichenbaum 1993, for a complete presentation) are intended to apply to both humans and animals and across all kinds of learning and memory tasks. In addition, it is critical to note that, ordinarily, both hippocampal system-dependent and independent mechanisms are available at all times to intact humans and animals and both can contribute to performance on virtually any task. One should expect to observe species and task differences to the extent that separate species are differentially inclined to utilize hippocampal system-dependent representations and to the extent that this form of representation is required to support different types of performance. Indeed, species differences are apparent in the general observation that human amnesia seems to be quite "global" whereas the impairment in animals with hippocampal system damage appears more limited. Apparent task differences are also prominent. For example, among the most frequently reported task differences is the severe deficit in spatial learning and apparent sparing of nonspatial learning in rats with hippocampal system damage. Nevertheless, while differences in the apparent *prevalence* of impairments across species and tasks are to be expected, careful behavioral assessments should reveal the same fundamental *character* of the impairment among species and tasks.

Expanding on this point with regard to studies on animals, the literature on the effects of hippocampal system damage in animals is voluminous and has been documented extensively elsewhere, at least with regard to many of the behavioral paradigms used in previous decades. Exhaustive tabulations and comparisons have revealed differences in the incidence with which deficits or sparing of function are reported on various categories of tasks (see Gray 1982; Gray & McNaughton 1983; O'Keefe & Nadel 1978). Nevertheless, for each such tabulation we were more impressed that impairment is not consistently associated with any particular task category. For example, a consideration of "simultaneous" versus "successive" discrimination reveals that in some experiments impairment was observed only on simultaneous discrimination (see sect. 4.2) and in other experiments only on successive discrimination (e.g., see also Gray & McNaughton 1983, Tables 20 & 22; Kimble 1963). In addition, other general variables by which tasks can be directly compared, such as task difficulty, also fail to be consistently associated with impairment. Thus, impairments are observed on both easy (that is, rapidly acquired) problems, such as the Morris water maze, spontaneous alternation, contextual learning, and difficult (that is, slowly acquired) tasks, such as some conditional discriminations. Furthermore, no impairment is observed on some difficult tasks, such as visual pattern discrimination, and impairment may or may not be observed on variants of tasks that are equivalent in difficulty, such as variations on odor discrimination learning (examples of each of these paradigms are cited below).

Moreover, we question the utility of straightforward tabulations because such an exercise inevitably leads to a sort of *psychoarithmetic* by which conclusions are made according to the simple majority of data. In our view, this approach ignores the scientific rule that even single examples and counterexamples within particular categories of paradigms are important and must be accounted for (see Cohen & Eichenbaum 1991; 1993). Conversely, we are impressed that a mixture of data is observed within virtually every learning and memory task. Our review of this literature (Cohen & Eichenbaum 1993) has shown that subtle variables can dramatically affect the representational demands within any behavioral paradigm. They do so by altering the relative contribution of processes that are dependent or independent of hippocampal involvement, by encouraging or hindering relational representations and by placing more or less demand on representational flexibility. Thus, in our view, it is fruitless to simply tabulate results from single variants on any paradigm.

Adopting a different approach, the distinctive properties of relational and individual representations can be captured in animals using properly designed behavioral testing paradigms that assess two critical aspects of memory representation. *First*, one can compare the performance of normal subjects with that of subjects with hippocampal system damage on variants of the same paradigm that either demand or hinder making compari-

sons and representing relationships among experiences with multiple items. Our account predicts that animals with hippocampal system damage will perform poorly when the demand for comparing and relating items is high, but they will perform at least as well as normal subjects when comparisons are deemphasized or hindered. *Second,* one can assess representational flexibility in the same subjects by requiring them to express successfully acquired memories in novel test situations. Our account predicts that, even when successfully learned, the memory representations of animals with hippocampal system damage will be inflexible such that they can be expressed only through repetition of the original learning experience.

To illustrate these ideas, what follows is a brief review of four general learning and memory paradigms that are currently under intensive experimental scrutiny in animal models of amnesia, and in which sufficient evidence exists to assess our predictions: sensory discrimination learning, place learning, working memory, and conditional and contextual learning. As with every other behavioral assessment used in this line of research, the data for each of these paradigms on the question of hippocampal involvement are mixed. As stated above, this state of affairs is fully expected from, and can be fully explained by, our view that the procedures of virtually any learning paradigm can be construed so as to encourage or hinder relational representation and to require or eliminate the need for representational flexibility. The experiments we emphasize are those that exemplify how a consideration of these properties of hippocampal system-dependent learning can clarify the pattern of impaired and spared performance within each paradigm. These data, together with parallel data from studies of various task performances in human amnesia, have been reviewed more completely elsewhere (Cohen & Eichenbaum 1993).

4.2. Sensory discrimination

The findings on discrimination learning involving specific, nonspatial stimuli have been reviewed extensively and are indeed quite mixed (e.g., Gray & McNaughton 1983, Tables 20 & 22; O'Keefe & Nadel 1978, Table A17). In some experiments, such as those involving the sensory discrimination tasks described above, the pattern of impaired and spared performance can be explained by differences in the memory delays or the memory load incurred when many items must be learned and remembered over the same period. However, in other studies temporal factors do not fully account for the pattern of performance. Instead, the pattern of performance by animals with hippocampal system damage can be related to differences in the representational demands across task variants.

For example, in our own work, we have observed impairment, no effect, or facilitation of learning on different variants of the same odor discriminations in rats with damage of the hippocampal system (Eichenbaum et al. 1988; 1989; Otto et al. 1991). In each variant of the task, the memory delays and load were similar, but other variables involving presentation of stimuli and response requirements were manipulated so as to alter the demand on relational representation and representational flexibility. First, we found that rats with fornix lesions were severely and persistently impaired in learning odor discriminations when they were required to choose between stimuli presented simultaneously and in close juxtaposition, thereby encouraging stimulus comparisons and selection among alternative stimulus choices. By contrast, they performed as well as, and sometimes better than, normal rats when the same stimuli were presented individually and successively on separate trials and no stimulus choice was required. Indeed, under conditions that strongly hindered comparisons between cues and eliminated differential choice responses, thus encouraging individual representations for each cue and biasing the execution of a single response, rats with hippocampal system damage outperformed normal rats. Second, we found that even under those conditions in which rats with hippocampal system damage succeeded in learning, their memory representations were abnormally inflexible. In one of our odor discrimination tasks, normal rats could identify familiar odors when "mispaired" in unusual configurations, but rats with hippocampal system damage performed as if presented with unfamiliar stimuli in such tests. Combined, these findings demonstrate the importance of determining the nature of the memory representation used by normal subjects, rather than focusing on the type of stimulus materials, formal description of the task, or even the magnitude of the initial learning impairment. Moreover, these results illustrate the usefulness of the two-stage strategy proposed above for assessments of relational memory processing and suggest that it can be used to sort out the mixture of results across the many variations of this paradigm.

4.3. Spatial learning and memory

Studies on spatial learning also involve a mixture of findings (see Gray & McNaughton 1983, Tables 21 & 25; O'Keefe & Nadel 1978, Tables A18 & A20). Here we will summarize two experiments in which the cues guiding performance were identical across variants of a task but other aspects of the cues or performance requirements were altered. One of these experiments involved variants of a plus-maze task where the location of a reward was guided by a set of extramaze cues (O'Keefe & Conway 1980). In both variants the rat began trials in any of three arms of the maze and had to go to a fourth "goal arm" as directed by the location of the cues. In one variant of the task the cues were distributed around the room and located between maze arms, thus encouraging the rats to use both the spatial relations among the cues themselves and relationships between the cues and the start position to guide performance. In the other variant of the task, the cues were clustered together and located just off the end of the goal arm, thus providing the view of a single compound cue, contiguous with the reward. Rats with hippocampal system damage were impaired in learning when the cues were distributed, but performed at least as well as normal animals when the cues were clustered. These findings are consistent with our view that variations in the arrangement of the same cues, so as to encourage a relational representation, confer an advantage to intact subjects over the limited strategies available to animals with hippocampal system damage, whereas providing an opportunity to adopt a bias towards a single, albeit complex, cue eliminates this advantage and makes the strate-

gies available to animals with hippocampal system damage as efficient as those that can be used by normal subjects.

A second study that used appropriate variations on a task involving identical spatial cues focused on spatial learning in the Morris water maze (Eichenbaum et al. 1990). In this paradigm the apparatus consisted of a tank three meters in diameter filled with water that was made opaque by the addition of milk powder (Morris 1984). A small escape platform was submerged just under the surface of the water so that it could not be seen by a swimming rat. On each training trial a rat began from one of four starting positions and learned to swim to the platform guided by various distal cues surrounding the water tank. This variant of the task strongly encourages the comparison of cues seen from the multiple views of the environment, and a representation of those cues in terms of their spatial relations and their relations to different start positions. Rats with hippocampal system damage were severely impaired in learning this version of the task (Morris et al. 1982). We developed a variant of the task in which the same arrangement of spatial cues was used but the demand for comparing views of the maze was eliminated by consistently starting the rat from the same start position, thus permitting subjects to adopt a bias in swimming toward a single, albeit complex, view in the test room. Under these conditions, rats with hippocampal system damage learned nearly as rapidly as intact rats. However, in subsequent testing where rats were required to navigate to the escape platform from novel starting positions, normal rats could use their representation of spatial relations among cues in the water maze but rats with hippocampal system damage performed poorly, sometimes never locating the platform in the otherwise familiar environment. Combining the results of this study and the O'Keefe and Conway experiment described above, both sets of findings show that either impaired or intact maze performance may be observed in rats with hippocampal system damage, depending on the extent to which subjects are encouraged to encode cues in terms of their spatial relationships. In addition, parallel to the findings on olfactory discrimination, these results show that even when rats with hippocampal system damage are successful, their representation does not support flexible memory expression. Finally, our review of the data on spatial learning suggests that the disproportionate reporting of deficits within this "modality" is a consequence of the extraordinarily strong demand that spatial processing puts on relational representation and representational flexibility; the findings do not require that hippocampal relational processing be unique to place learning.

4.4. Working memory tasks

Working memory, as defined by Olton et al. (1979), refers to memory that is useful for only a single test trial. Superficially, it might seem that the relevant memory demand in working memory, especially for nonspatial stimuli, focuses on intermediate-term storage and recognition of individual stimulus items, similar to the demands of the DNMS tasks described above. However, a more thorough comparison of the representational demands of working memory and DNMS tests indicates that working memory requires a relational representation.

To understand how the working memory component of performance in the nonspatially cued radial arm maze also requires a relational representation, it is important to consider the differences in the working memory demands of this task compared with the kind of memory required in recognition paradigms like the DNMS tasks discussed above. Consider, for example, the behavioral paradigm widely used to test working memory capacity – the radial arm maze task. The apparatus involves an elevated maze comprising a set of arms radiating from a central platform like spokes on a wheel. On each trial all of the arms are baited and the rat is allowed to retrieve the rewards. The most efficient foraging strategy involves remembering which arms have been entered and not revisiting those arms within a trial. The available cues that guide performance are either spatial ones provided by the extra-maze environment or visual and/or tactile cues that distinguish the maze arms. In either variant of the task, within each trial; all the cues are typically available throughout performance the rat is not prevented from seeing the cues between making its delayed choices. Consequently, remembering the stimuli that identify each arm is not required. Rather, what must be remembered during a trial are the behavioral events associated with entering each arm; that is, rats must remember their previous episodes of entering arms, in addition to, or instead of, remembering the distinguishing qualities of the arms themselves. By contrast, recognition memory in tasks using trial-unique or infrequently presented single cues can be accomplished by a direct perceptual match between test stimuli and a memory representation of the sample stimulus, that is, by remembering and recognizing the stimulus itself without necessarily remembering the episode of interacting with the sample.

Thus, in our view, working memory involves the encoding of specific "episodes" associated with perceptually defined maze arms and not a perceptual trace of the arm itself (cf. Olton 1984). The events that characterize each episode in working memory are defined in terms of how they compare and contrast with other experiences with the same stimuli. As such, episodic memories clearly exhibit the properties of relational representation. This is not to say that it would be impossible to guide performance in working memory tasks on the *relative* familiarity of cues; presumably arms with distinctive cues visited within a session would have stronger relative familiarity than arms not visited in that session. Individual representations based on the enduring strength of decaying sensory representations might be used to support performance even when memory for the previous episodes within a session is unavailable. Consistent with this possibility, rats with hippocampal damage are only modestly impaired, or impaired only on some variants of the nonspatial radial arm maze task (Jarrard 1986; Nadel & MacDonald 1980; Winocur 1982).

The pattern of performance on several other spatial and nonspatial tasks is explained by a strong working memory component. For example, Thomas and Gash (1988) used a T-maze task that involved both a consistent reward association (always go right at the first choice point) and a working memory component (turn in the direction opposite to that last taken at the second choice point). Hippocampal system lesions had no effect on the consistent component but resulted in severe impairment on the

working memory component. This finding is reminiscent of the frequent (but unreliable) finding that rats with hippocampal damage normally learn simple spatial discriminations in a T- or Y-maze but are impaired on spontaneous or learned alternation guided by the same available cues (O'Keefe & Nadel 1978 – compare Tables A15, A16 & A25). Rats with hippocampal system damage are also impaired on performance in a go/no-go alternation task (Winocur 1985; 1991; see also Jarrard 1975) and in delayed matching to sample guided by trial-repetitive brightness cues (Foster & Rawlins 1992; Raffaele & Olton 1988; Winocur 1992). It is noteworthy that severe impairments are also observed on other tasks that do not require working memory (e.g., the conventional version of the Morris water maze), indicating that the demand for working memory is not a prerequisite for hippocampal involvement. However, as these findings show, hippocampal system function is required for normal performance in both spatial and nonspatial tasks where there is a strong demand for working memory.

4.5. Conditional and contextual learning

A large number of studies have used variations of conditional and contextual learning tasks, and the use of these tasks has come under considerable scrutiny only in recent years. As will be shown, however, reports on the effects of hippocampal system lesions on this collection of paradigms are mixed, as was the case with the other paradigms described above (e.g., see Jarrard 1993). Nevertheless, in our view, these data can be reconciled by considering the demand for relational representation in variants of the tasks employed.

Conditional learning tasks are like sensory discriminations except that the reward assignments for particular cues depend on the presence of another cue. In some cases the conditional cue is itself a specific stimulus, appearing concurrent with or prior to a punctate "explicit" cue that is presented just prior to a reinforcer; in other cases the conditional cue involves "background" stimuli (i.e., the context) present throughout a particular training session. In all such tasks, explicit cues are presented both with and without a conditional cue, or their combination constitutes the conditional cue, and the multiple stimulus situations must be differentiated in accordance with the conditional cue(s). One might presume that conditional and contextual learning paradigms provide particularly good tests of our account because these types of learning tasks would seem to require the encoding of relationships between explicit cues and other conditional cues, or a context that might be mediated through hippocampal-dependent mechanisms. There are, however, other ways in which conditional and contextual cues can be encoded that do not require relational representation. In some situations conditional cues can act as general "facilitators" that signify an increased probability of reinforcement for any following stimulus. The mechanisms of such facilitation would be expected to involve the acquisition of response biases independent of hippocampal involvement. In other situations, conditional cues can be fused with the explicit cue to form a compound or "configural" stimulus. To the extent that explicit cues can be encoded along with conditional or contextual cues as distinguishable compounds, learning guided by unique configural cues could also be supported by individual representations through hippocampal system-independent mechanisms for the recognition and acquisition of biases, just as discussed earlier with regard to sensory discrimination (see sect. 4.2). Assuming that subtle task parameters might alter the extent to which subjects encode the cues in terms of relationships between perceptually independent stimuli, as opposed to general facilitators or unique configural stimuli, one would expect the literature on conditional and contextual learning to be mixed with regard to the effects of hippocampal lesions. Such is indeed the case. Different investigators, using different variations of these tasks, have found contradictory results and reached opposite conclusions.

One might conclude that this state of affairs renders studies on conditional and contextual learning useless with regard to the goals of this review. There are, however, ways to characterize the nature of representation used in conditional and contextual learning, specifically through tests for general facilitation (sect. 4.5.1) and for the property of compositionality described earlier in the distinction between relational and individual representations. If the representation used during learning is indeed relational, subjects should still be able to recognize and respond appropriately to the individual cue elements in accordance with the specific acquired relationships. Conversely, if the representation is configural, subjects would not be expected to recognize stimulus elements in isolation. Some of the paradigms used in conditional and contextual learning preclude such an analysis, such as when all presented combinations of cue elements are differentially reinforced during original training. In other paradigms, however, probe tests directed at the nature of representation have shown that animals with hippocampal system damage sometimes use an abnormal configural strategy (as will be seen in sect. 4.5.2 below,), consistent with our view that configural representations occur independently of hippocampal function. These findings suggest that animals with hippocampal system damage actually resort to configural representations in the absence of the capacity for relational processing.

The distinctions between "relational" and "configural" representations and "facilitators" in conditional and contextual learning can best be illustrated by considering examples of several variants on these paradigms. We will discuss examples of both conditional learning tasks, where subjects are required to use the conditional cues to distinguish ambiguous explicit cues, and contextual learning tasks, which involve a set of static background cues that are not varied during training and thus are only incidental to the explicit cue and its consequences. (Such cues are typically altered only in a post-training test phase.)

4.5.1. Conditional learning tasks. Three different general variants of conditional learning have been reported. In one of these, called Pavlovian feature-positive conditioning, an explicit cue is followed by reinforcement only if it is preceded by or occurs concurrently with another, conditional, cue. For example, in a study by Ross et al. (1984), the presentation of a tone was followed by the delivery of a food reward only if this cue was preceded by a conditional light cue; thus the light was a conditional cue for the efficacy of the tone. Rats with hippocampal system

damage were severely impaired in acquisition of the conditional response but acquired normal discriminative responses to other simple, that is, nonconditional stimuli (a clicker and a noise). Jarrard and Davidson (1990; 1991; Davidson & Jarrard 1989) confirmed these results when the lesion involved aspirations of the hippocampus, but not with more selective neurotoxic lesions. Furthermore, they showed that the conditional cue acted as a general facilitator of responding to any cue of ambiguous significance, rather than as an element of either a specific relational or configural representation with the explicit cue, at least in their variant of the task. Thus, this paradigm probably does not serve to test the relational (or configural – see below) hypothesis.

A more valid test may have been provided in a study by Gallagher and Holland (1992), who used a variant of this task in which two auditory cue elements served as CS+ and CS− cues, and a panel light conditional cue presented along with the explicit cue served to reverse the valence of each on some trials; the task thus included both "feature-positive" and "feature-negative" properties of the conditional cue, making it unlikely that the conditional cue could serve as a general facilitator or inhibitor. Indeed, in separate experiments, Holland (1991) has shown that such training does involve specific configural representations of the conditional and explicit cues. Notably, Gallagher and Holland (1992) failed to replicate the Ross et al. (1984) results using this paradigm, although comparison of the results across these studies is obscured by the fact that Gallagher and Holland also used the more selective type of hippocampal system lesion. These findings are consistent with our proposal that subtle alterations in task procedures can dramatically change the nature of the memory representation used from one that demands hippocampal function to one that does not. Further evidence, more directly supporting this notion, is the finding that whether or not animals with hippocampal lesions were impaired on feature-positive conditioning in an eyeblink conditioning task depended on which of the two cues was the conditional cue and which was the explicit one (Loechner & Weisz 1987). In addition, for at least some variants of this paradigm, selective neurotoxic lesions of parts of the hippocampal formation produce weaker effects than more complete hippocampal formation lesions produced by other methods. The issue of complete versus partial hippocampal formation lesions (see sect. 1.2) has been especially problematic for interpreting discrepancies in the findings on conditional learning. Of particular value would be studies that examine the effects of selective neurotoxic lesions of the entire hippocampal formation – that is, the hippocampus, dentate gyrus, and subiculum.

A second variant on conditional learning is the negative patterning paradigm (Sutherland & Rudy 1989). In this task there is no separate conditional cue; rather, subjects are trained to distinguish the separate presentation of two cue elements (i.e., a light and a tone), each associated with reinforcement for an operant response, from the simultaneous presentation of the combined cues, which predicts nonreinforcement. In their original study using this task, Rudy and Sutherland (1989) reported that rats with hippocampal system damage could not acquire the negative patterning task even though they performed normally on a simple discrimination between the light and a different tone. Davidson et al. (1993), however, failed to replicate this result, regardless of whether the lesion method involved their highly selective neurotoxic technique or the same less selective lesion technique of Rudy and Sutherland (1989). The failure to replicate may be attributable to procedural differences between the tasks (i.e., specific differences in the response requirement) that resulted in different representational strategies by the subjects. Overall, the mixture of results across studies on feature-positive/feature-negative and negative patterning tasks serves to highlight the need for closer examination of specific training procedures as well as lesion methods. Nevertheless, in both the Davidson et al. (1993) and Gallagher and Holland (1992) studies, it seems likely that configural representation rather than general facilitation/inhibition was used by rats, suggesting that the hippocampus itself may not be required for this form of representation and thereby explaining the failure of these investigators to find hippocampal lesion effects (see below).

A third variant on conditional learning will here be termed "conditional discrimination." In several variations on this task, multiple conditional cues serve to qualify the reward associations of subsequent explicit cues. In an early variant of this task (Kimble 1963), the color of a Y-maze (white or black) qualified the placement of a reward in the left or right arm of the maze. In other experiments (Hirsh 1974; Hsiao & Isaacson 1971), the motivational state of the animal (hunger or thirst) predicted the placement of reward in a T-maze. In more recent variants on this task, Sutherland et al. (1989) used the illumination condition of a start box in a Y-maze to qualify whether a reward would be located in a white or black goal arm, and Whishaw and Tomie (1991) used the odor of a string to signal whether pulling a thick or thin string produced a reward. In each of these tasks, animals with hippocampal system damage were impaired in learning the conditional discrimination while, at least in the more recent studies, the same animals demonstrated normal learning of simple discriminations guided by the same cues.

In other studies on spatial and nonspatial conditional discriminations the effects of hippocampal system damage were also mixed (e.g., Markowska et al. 1989). Most relevant to the views expressed here was the finding that monkeys with hippocampal system damage were impaired when required to use the location of explicit cues in a visual scene as the conditional cue, but unimpaired when required to use different places in the test room composing completely different background scenes as the conditional cue (Gaffan & Harrison 1989; Murray et al. 1989). Combined with the findings from other studies of conditional discrimination described above, the results strongly implicate hippocampal system function in nonspatial conditional discrimination learning, although too little work has been done to characterize the form of representation used in any of these paradigms.

4.5.2. Contextual learning tasks. In studies on contextual learning there is also a mixture of findings in the area indicating either sparing or impairment of learning capacity. Furthermore, across variants on this paradigm hippocampal system damage can result in either impaired or abnormally strong utilization of contextual cues. Some

studies use paradigms where the retention of a conditioned response is dependent on context, such that in intact animals good retention is observed when they are tested in the same context used during initial learning, and poor retention is observed when the context is changed. For example, Penick and Solomon (1991) found that classically conditioned eyelid responses are context dependent in normal rabbits, and Good and Honey (1991) described various forms of appetitive conditioning that are similarly context dependent in normal rats. In both studies, animals with hippocampal system damage failed to demonstrate context dependency. In addition, during conditioning of fearful responses to an explicit cue (typically a brief tone) there is an incidental conditioning to the contextual stimuli, observed as increased fearful behaviors when the subject is reexposed to training context without or prior to another presentation of the explicit cut. In this paradigm, hippocampal system damage results in poor conditioning to the context even though conditioning to the explicit cue – even when presented in a different context – is spared (Kim & Fanselow 1992; Phillips & LeDoux 1992; Seldon et al. 1992). It is important to note that rats with hippocampal system damage condition normally to the context when the explicit cue is omitted during training, indicating that the processing of the same contextual cues is possible even in the absence of hippocampal function (Phillips & LeDoux 1992). This finding clearly demonstrates that the hippocampal system is not required for processing either the explicit cue or the context but is critical for normal representation of the relationship between these cues.

The story on contextual learning becomes more complicated when one considers other findings indicating that, in other training paradigms, animals with hippocampal system damage show abnormally strong dependence on contextual cues. For instance, Winocur and Olds (1978) reported that rats with hippocampal system damage showed abnormally poor retention of a pattern discrimination when tested in a different context, and conversely, abnormally good performance in reversal of the discrimination in a different context. Winocur et al. (1987) also reported that whereas normal rats show an aversion to an environment proportional to the probability of a CS predicting shock, rats with hippocampal system damage conditioned strongly to the environment at all levels of shock predictability.

The mixture of results across these variants of contextual learning paradigms makes it clear that the explicit cues and contexts can be related to one another using different forms of representation, leading to opposite effects of hippocampal system damage. It appears that, in situations where the explicit cue is particularly salient with respect to the context, animals with hippocampal system damage condition extraordinarily well to these cues, a phenomenon reminiscent of enhanced conditioning of individual associations in some discrimination paradigms (see above). To the extent that this occurs, the observed context dependence in animals with hippocampal system damage might be reduced. Conversely, in situations where the explicit cues are not strongly salient over contextual cues, animals with hippocampal system damage might be abnormally inclined to encode both types of cues as a configural cue, making performance overdependent on the presentation of their combination during testing. An abnormal tendency to encode cues this way was observed when discriminative cues were closely juxtaposed in monkeys (Saunders & Weiskrantz 1989) and in rats (Eichenbaum et al. 1989). In both studies, animals with hippocampal system damage, unlike intact animals, failed to recognize familiar discriminative stimuli when they were presented in novel combinations; that intact animals could handle the familiar stimuli in novel combinations indicated that they had stored relational representations of the perceptually independent cues, with compositionality, and could use the relational representations flexibly to make novel judgments. These results, combined with observations of intact configural association in some of the conditional learning tasks described above, support our suggestion that the acquisition of configural representations is accomplished outside the hippocampal system. Conversely, the combined findings support the notion that the hippocampal system is critically involved in representation of perceptually independent stimuli in terms of their relevant relationships.

4.6. Summing up about paradigms used in assessing the representational distinction

Despite the many differences in procedures used between and within the various paradigms, and despite the absence of conclusive data on the nature of the representation used by normal animals in many of these tasks, some general conclusions can be drawn from the neuropsychological studies (see Cohen & Eichenbaum 1993, for a more complete treatment). First, impairment or intact performance may be observed on virtually any learning paradigm depending on the nature of task parameters that encourage comparing and contrasting items and representation of the relevant relations between them. Second, even when successful in learning, animals with hippocampal system damage are severely restricted in the flexibility of their expression of learned performance. The demand for flexibility is implicit during training in some tasks, for example, in the conventional version of the Morris maze task, where the starting position is varied across trials, and in working memory tasks, where the significance of familiar cues is constantly changing. In other tasks, such as discrimination learning and some conditional and contextual learning paradigms, learning often proceeds normally and the inflexibility of hippocampal system-independent representations is revealed only in tests that probe the nature of the successfully acquired memory. Nevertheless, examples of spared learning with representational inflexibility can be observed across all paradigms.

4.7. Critical contribution of all hippocampal system components to relational representation

A major prediction of our two-stage model is that the hippocampal formation itself becomes critical to performance whenever the task requires relational processing; however, our model predicts that damage to the cortical areas surrounding the hippocampus will also produce deficits on these tasks, because hippocampal processing depends upon associations with neocortex that are mediated through these areas. Consistent with these predictions, lesions limited to the hippocampal formation or

fornix result in severe impairments in monkeys on tasks involving spatial cues (Mahut 1972) on conditional discriminations involving the configurations of scenes (Gaffan & Harrison 1989; Murray et al. 1989), or on the flexible expression of object associations (Saunders & Weiskrantz 1989). The data from a large number of experiments on rats parallel these findings. Selective hippocampal ablation, fornix transection, or damage to the parahippocampal region have all been reported to result in severe impairment on performance in learning and memory tasks that involve sensory discrimination, spatial learning, working memory, and conditional or contextual learning (see reviews by Barnes 1988; Gray & McNaughton 1983; Levisohn & Isacson 1991; O'Keefe & Nadel 1978; Olton et al. 1979), and on the flexible expression of odor- or place-guided memory (see Eichenbaum 1992; Eichenbaum et al. 1992a).

In experiments directly comparing the effects of fornix lesions and/or removal of the complete hippocampal formation with that of parahippocampal damage, equivalent deficits were observed on measures of spatial working memory (Aggleton et al. 1992; Jarrard 1986; Olton et al. 1978; 1979; 1982). In addition, nonspatial working memory can be impaired after damage limited to the hippocampal formation, as well as after damage to the parahippocampal region (Cho et al. 1992; Jarrard 1986; Nadel & MacDonald 1980; Olton & Feustle 1981; Winocur 1982). Similarly, selective damage to the hippocampal formation or fornix impairs performance on DNMS tasks involving the same two spatial (Aggleton et al. 1986) or nonspatial (Raffaele & Olton 1988) cues on each trial. Even though these paradigms use procedures similar to those employed in tests of recognition memory, they emphasize working memory rather than recognition memory because the same cues are used repetitively on each trial, minimizing the usefulness of perceptual familiarity as a cue (cf. Rawlins et al. 1993). Thus in both monkeys and rats, the data consistently indicate that the entire hippocampal system – that is, the hippocampal formation, its subcortical connections through the fornix, and the adjacent parahippocampal region – is required to support relational representation.

4.8. Intermediate-term storage of relational memories

Earlier in this review we distinguished a selective role for the parahippocampal region in the intermediate-term storage of individual representations from the involvement of the hippocampal formation in relational memory processing. This leaves open the question of whether the parahippocampal region itself can support intermediate-term retention of *relational* as well as individual representations in the absence of normal hippocampal function or whether an intact hippocampal formation is required for this aspect of memory as well. The answer seems to be that processing within the hippocampal formation plays a critical role in the establishment of relational representations even for intermediate retention periods. Thus, intermediate-term recognition memory for places, or relations between particular objects and places, are impaired after damage to the hippocampal formation or fornix just as they are after damage to the parahippocampal region. For example, selective ablation of the hippocampal formation impairs delayed recognition of the place where an object was previously seen (Parkinson et al. 1988). Transection of the fornix results in selective impairment on delayed spatial and conditional spatial tasks (e.g., Mahut 1972; Murray et al. 1989). Selective hippocampal lesions also result in a severe deficit in rats performing delayed match-to-place tasks in the water maze and Y-maze, and in spatial nonmatching and memory for the order of arms visited on the radial maze (Kesner & Novak 1982; Morris et al. 1990; Olton 1986; Olton et al. 1979). Selective hippocampal lesions also result in delay dependent impairment in intermediate-term memory for nonspatial information in delayed go/no-go alternation (Jarrard 1975; Winocur 1985; 1991), in nonspatial matching, and nonmatching to sample with trial-repetitive cues (Raffaele & Olton 1988; Winocur 1992), and in delayed responding on a conditional discrimination (Winocur 1991). In many of these tasks, performance that requires only short-term memory has been shown to be spared, indicating that hippocampal function is not required for relational judgments *per se*, but rather for memory based on such judgments.

In addition, there are other behavioral paradigms in which the critical cues would seem superficially not to require relational representation, yet for which damage to the hippocampal formation results in a severe deficit in intermediate-term retention. We will consider two such paradigms here: timing and trace classical conditioning. For each of these, the relevant behavioral tasks were ostensibly created to test memory capacity for single stimulus events. We will argue, however, that according to a careful analysis the critical memory processes supporting performance in these tasks probably require relational processing rather than, or in addition to, storage of single perceptual representations, thereby bringing these data into line with the model presented here.

4.9. Timing

Rats with damage to the hippocampal formation or fornix are impaired on tasks that require responding at a specific minimum interval following a previous response – in other words, timing. In one task that is often used to study the neural substrates of timing, rats receive differential reinforcement for low response rates (DRL) of an operant behavior (typically a bar press). This task requires simply that a rat wait for a fixed period between each behavioral response in order to receive a reward; premature responses reset the reinforcement schedule. Rats with hippocampal system lesions are severely impaired on this task if the waiting period is long enough and the response time is unsignalled (e.g., Boitano et al. 1980; Braggio & Ellen 1976; Clark & Isaacson 1965; Sinden et al. 1986); the deficit is apparent whether or not rats are allowed to participate in "collateral" behaviors that might exploit hippocampally dependent, spatially defined behaviors to bridge the waiting period (Rawlins et al. 1983). These findings, combined with other data indicating that rats with hippocampal system damage demonstrate a foreshortened timing function when rewarded for responses at a fixed minimum interval (Meck 1988; Meck et al. 1984; Olton et al. 1987), indicate that the hippocampal formation is important for accomplishing internally based timing.

No studies have compared the effects of damage to the

parahippocampal region and the hippocampal formation on DRL or other timing tasks. Nevertheless, to the extent that timing requires only the representation of an isolated stimulus event, the severity of the impairment after selective hippocampal formation or fornix lesions would seem to call into question our contention that the hippocampal formation is not critical to memory for single isolated cues. However, one important consideration involves the nature of the event that is remembered over the timed interval and how this memory supports timing. Our view is that the remembered event in timing tasks probably involves a relational rather than an individual representation. Although it is not clear what event is being remembered in DRL, note that all the perceptual stimuli that could be used are available throughout the memory delay period. Thus, as was the case with working memory tasks, it is the behaviorally defined episode with such stimuli, and not the memory of any particular stimulus item, that apparently drives performance. As concluded above for working memory tasks, such episodic memories probably depend on a relational representation and therefore on the integrity of the hippocampal system (see Cohen & Eichenbaum 1993).

4.10. Trace conditioning

Another finding that is superficially incongruous with our model is that damage to the hippocampal formation disrupts "trace" but not "delay" classical conditioning of the eyeblink response in rabbits (Moyer et al. 1990). Understanding how the hippocampal formation itself and the kind of representation processed in the hippocampus might contribute to trace classical conditioning requires a consideration of the processing requirements and anatomical pathways supporting different forms of classical eyelid conditioning. In the standard delay version of the conditioned eyeblink task a tone CS precedes and overlaps with a UCS that evokes a reflexive eyeblink. Under these conditions, learning to blink during the presentation of the CS and prior to UCS onset occurs gradually and hippocampal damage does not affect learning. This is consistent with the view that the hippocampal system is not critical to the acquisition of learned responses to individual stimuli (see above). In contrast, if the duration of the CS onset is abbreviated so as to create a 500 msec gap between CS offset and UCS onset (trace conditioning), hippocampal lesions result in a severe and lasting conditioning impairment (Moyer et al. 1990; Solomon et al. 1986).

The neuroanatomy of hippocampal-brainstem connections provides an insight into how information acquired by the hippocampus could contribute to this form of conditioning. Converging data indicate that the pathways supporting classical eyelid conditioning are localized in the brainstem and that acquisition is subserved by neural plasticity within the cerebellum (Krupa et al. 1993; Thompson 1986). Unit recording studies, however, have demonstrated that the hippocampus receives and processes information about stimulus events associated with eyeblink conditioning in both the delay (Berger et al. 1976) and trace (Solomon et al. 1986) versions of the task. The hippocampal representation is not a simple stimulus-elicited activity but, in the early trials of trace conditioning, involves the activation of some form of neural representation at the offset of the CS that persists throughout the trace interval (Solomon et al. 1986). Thus the hippocampus forms and maintains a representation of the stimulus events in this task even though a specifically relational representation is not required in this type of learning. This representation can reach the cerebellar circuit via multisynaptic projections involving subicular-mammillary and septal-habenular pathways to the ventral pontine and cerebellar nuclei (Berger et al. 1986). In this way the hippocampal representation of the CS is *available* to the cerebellar circuit, and its lasting nature could serve, in place of a CS, as a cerebellar associative mechanism that requires CS-UCS contiguity. When CS-UCS contiguity is broken, the hippocampal system contributes a CS-elicited representation that persists for the trace interval and is thus contiguous with the UCS. When this representation is prevented by a hippocampal lesion, no other contiguous stimulus is available and conditioning is prevented. We assume that neural activity in the hippocampus reflects the representation of particular stimulus episodes even though a relational form of representation *per se* is not required and makes no special contribution to trace or delay classical conditioning. Nevertheless, the persistence of this representation can be exploited to satisfy the contiguity requirement imposed by CS-US gap in the trace conditioning paradigm.

Collectively, the observations on place recognition, spatial and nonspatial working memory, and timing are consistent with our hypothesis that hippocampal processing makes a significant contribution to memory processes in a variety of circumstances in which intermediate-term retention depends on representating relations among cues (e.g., spatial memory and object relations) or on specific episodes with familiar stimuli (working memory and timing). In addition, the data on classical conditioning suggest a mechanism by which a persistent hippocampal representation may be exploited to bridge a brief temporal gap in the absence of explicit CS-UCS temporal contiguity. Conversely, the circumstances in which the parahippocampal region can support memory in the absence of normal hippocampal function are limited to tasks in which current stimuli can be matched to an iconic (i.e., perceptually based) representation that can be used to make a perceptual familiarity judgment.

5. Neural coding in the neocortex and hippocampal system during memory performance

Our model of the sequential stages of hippocampal processing is further supported by observations on the behavioral physiology of single neurons in both the parahippocampal areas and the hippocampus itself, as well as in the neocortical areas that provide the critical information upon which the hippocampal system operates. The relevant data derived from several studies examining the functional correlates of cortical and hippocampal activity in either rats or monkeys performing various memory tasks involving different stimulus modalities. In addition, there is a lack of clarity with regard to the site of recordings in the transitional areas between visual-temporal and perirhinal-parahippocampal cortex, making tentative our designations of the boundaries of areas with particular

coding properties (see below). Nevertheless, to the extent that the results of these studies can be combined, the findings consistently indicate that there are three distinct patterns of physiological activity in single neurons that can be related to memory processing, and that each of these patterns and associated characteristics of neural coding is consistent with the processing functions assigned to specific stages in the model proposed here. These data indicate that the neocortex can support very short-term storage of specific information, that the parahippocampal area supports an intermediate-term store, and that the hippocampal formation does not store specific sensory information but rather supports relational processing.

5.1. Labile neocortical representations of individual items and events

With regard to neocortical association areas, a number of studies have revealed two different forms of memory representation by which neocortical cells sustain specific stimulus or motor encodings over short delay periods in recognition memory tasks (e.g., Fuster 1990; Fuster & Alexander 1971; Fuster & Jervey 1981; Goldman-Rakic et al. 1990; Mikami & Kubota 1980; Miyashita & Chang 1988; Niki & Watanabe 1976; Sakurai 1990b). One type of memory correlate might reflect an "active" representation of specific sensory events in the form of evoked neural responses that are sustained during the memory delay period (Figure 4a, top). For example, in monkeys performing visually cued DMS tasks. Fuster and Jervey (1981; also Fuster 1990) and Miyashita and Chang (1988) described cells in the inferotemporal cortex that responded to the onset of sample stimuli and persisted in firing at elevated levels throughout a memory delay period during which the subject had to retain information about the stimulus in order to perform a subsequent matching response. Both stimulus-driven and delay activity in many of these cells were selective to a particular visual pattern or stimulus characteristic. In addition, several experimenters recording from monkeys performing delayed alternation and delayed response tasks have observed cells in the prefrontal area that fire at the onset of sample cues and throughout the delay period with stimulus- or behavior-selective activation. For example, Goldman-Rakic et al. (1990) described prefrontal cells that persisted in firing during the delay interval, encoding the position of either a particular sample stimulus or a particular intended behavioral response that was withheld during the delay. Sakurai (1990b) described auditory cortex cells in rats performing a tone-cued DNMS task that, like inferotemporal and prefrontal cells in monkeys, demonstrate stimulus-selective responses that persist throughout a memory delay period.

The other type of memory correlate described in neocortex studies might reflect a "passive" memory representation characterized by a strikingly reduced responsivity to familiar stimuli. For example, Baylis and Rolls (1987, Figure 4a, bottom; see also, Rolls et al. 1989a) described visually responsive cells in inferotemporal cortex that fired much less to a stimulus item on its immediate repetition in a serial recognition task. Furthermore, the reduction in responsiveness was, in some cells, greatest for the neuron's optimal stimulus as compared to other items, demonstrating the same item-specificity that characterizes "active" neocortical memory correlates (Baylis & Rolls 1987; E. K. Miller et al. 1991b; 1993). Superficially, the concept of *reduced* activation serving as the substrate for memory storage seems counterintuitive. Indeed, the reduction in responsiveness of inferotemporal cells to repeated stimuli has been characterized simply as an extraordinarily rapid form of habituation (E. K. Miller et al. 1991a). However, positron emission tomography (PET) data from human subjects observing visually presented words (Squire et al. 1992) suggest a different interpretation. Squire et al. found that metabolic activation in an area of human visual cortex is diminished when subjects view familiar material during the retention phase of a priming task. In their interpretation of these data, they argued that diminished activation to familiar material may reflect a reduction in the neural processing or the number of neural computations required for the reidentification of items that have been recently processed. Extrapolating to the level of individual neurons, the same account could explain the reduced "responsiveness" of neocortical cells to familiar stimuli – the decrement in stimulus-elicited firing reflects a diminution in the circuit activity required for stimulus reidentification. Thus "passive" memory correlates might reflect the phenomenon of "priming" in the neural circuits that process perceptual information.

Both types of neocortical memory representations can be quite labile. What we have called active cellular responses do not outlast the trial in which the information must be retained (e.g., Fuster & Jervey 1981). Similarly, in some areas or tasks, the above described passive correlates cannot be sustained across substantial perceptual interference. Thus, Baylis and Rolls (1987; see also Rolls et al. 1989a) reported that the reduction in responsiveness of inferotemporal neurons that normally occurred after a single exposure to a particular stimulus was abolished by the presentation of a different item. Some qualifications about the lability of passive responses and a possible distinction with active responses were recently revealed in a study using a delayed match to sample task where the sample stimulus is followed by a series of choice cues. In this paradigm, active memory responses were abolished by the presentation of another stimulus, but passive memory responses were observed to persist through the presentation of intervening nonmatching choice cues presented within the same trial (E. K. Miller et al. 1993). In another study, active visual responses in cortical area V4 were observed to withstand interference from the presentation of other stimuli when the animal was required to remember a sample pattern while examining a series of test patterns within each trial (Maunsell et al. 1991). Notably, both the passive and active memory responses observed in these studies disappeared *between* trials. In the E. K. Miller et al. (1993) study, this effect was not explained by the mere passage of time, indicating that the responsiveness of visual cortical cells is "reset" when the information is no longer relevant. By contrast, in the Baylis and Rolls (1987) study, response decrements were abolished by a single intervening stimulus in a serial (running) recognition task where the monkey had to remember stimuli across a variable number of trials. The discrepancy between these findings might be related to relatively subtle differences in the visual stimuli or train-

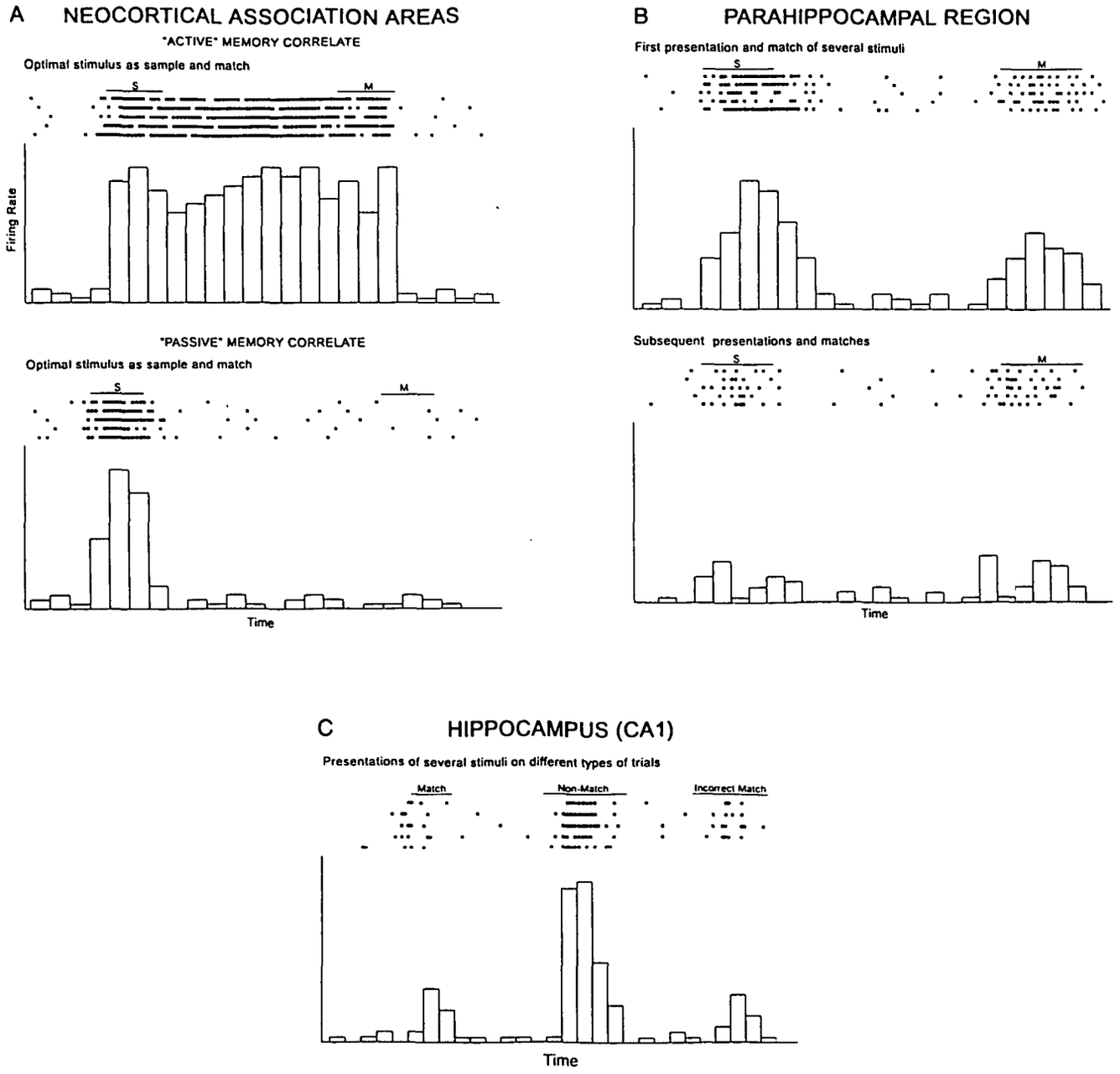

Figure 4. Different types of memory correlates of neural activity in (A), the neocortex (data adapted from: [top] Miyashita & Chang 1988, and [bottom] Baylis & Rolls 1987), (B), the parahippocampal region (data adapted from Riches et al. 1991), and (C), the hippocampal formation (data adapted from Otto & Eichenbaum 1992b). The top portion of each panel portrays a raster display of example trials, below which is plotted a summary histogram of firing rate. A and B involve discrete trials of delayed nonmatch-to-sample (DNMS) performance, so neural activity is shown before and after the sample stimulus presentation (S), match stimulus presentation (M), and the intervening memory delay. In C, the continuous delayed nonmatch-to-sample (cDNM) task involved a continuous sequence of stimulus presentations; hence each stimulus presentation is identified by its relation to the previous item. The data for each example are selected from the references cited and are normalized for both firing rate and time scale to facilitate comparisons.

ing procedures, but this pattern of findings might also reflect differences in locus of the recordings. Baylis and Rolls recorded primarily from cells in lateral inferotemporal cortex (in or near the superior temporal sulcus) whereas E. K. Miller et al. recorded from the anterior inferotemporal area adjacent to the parahippocampal region. Furthermore, despite differences in the short-term lability of responses to single stimulus presentations, many cells in both parts of inferotemporal cortex exhibit a gradual cumulative decrement in responsiveness to items repeated many times across a testing session, suggesting that multiple experiences with a stimulus can modify the representation for longer durations (see also Riches et al. 1991; Rolls, et al. 1989a). In sum, the coding properties of neocortical association cortex could support a short-term memory for single stimulus presentations using both active and passive item-specific representations but, particularly for areas distant from the parahippocampal region, these representations are short lasting and susceptible to interference; only with extended experience can

these areas support recognition over delays of longer than several seconds.

5.2. Intermediate-term storage of specific events in the parahippocampal region

Unlike cells in the neocortex, those in the parahippocampal region do not display active, sustained responses over memory delays. However, like neocortical association areas, parahippocampal neurons demonstrate passive memory representations in the form of stronger stimulus-elicited responses to novel versus familiar stimuli. Furthermore, passive cellular memory representations in perirhinal and entorhinal cortex, like those in inferotemporal cortex, are often stimulus-specific. For example, Riches et al. (1991) observed these properties in cellular activity recorded from the entorhinal cortex and, to a lesser extent, from the inferotemporal cortex of monkeys performing a DNMS task. They described cells that demonstrated stimulus-selective visual responses, and many of these cells responded more to a visual cue when it was the sample than when it immediately reappeared as the match stimulus. Similarly, Sakurai (1990b), recording from entorhinal cortex in rats performing a tone-cued DNMS task, described cells with stimulus-specific, sensory-elicited responses. In neither of these studies was delay-related activity in the parahippocampal region observed.

These studies show that, in contrast to most neocortical association areas, passive representations in the parahippocampal and immediately adjacent anterior inferotemporal region (AIT) might be relatively insensitive to interference resulting from the presentation of intervening items and trials. Brown et al. (1987; Riches et al. 1991) reported that neurons in parahippocampal region and AIT continued to exhibit reduced responsiveness to familiar stimuli even when other stimuli were presented during the period between an initial stimulus presentation and its repetition (Figure 4b). Again, there are some inconsistencies in the data across experiments; unlike E. K. Miller (1993), Riches et al. (1991) did not observe a resetting of responsiveness between discrete trials in AIT cells. The discrepancy possibly may be due to differences in the visual stimuli or testing procedures. However, it is also possible that the discrepancy can be related to our poor understanding of the functional boundaries between visual-perceptual processing areas and the parahippocampal region. Here, we will not take a firm position on whether there is a discrete functional boundary; in accordance with the view favored by E. K. Miller et al. (1993, p. 1474), we will conclude simply that the *closer* to the perirhinal region the longer lasting the passive representation. To the extent that this proves to be the case in more extensive comparisons, passive memory representations in the parahippocampal region (and in adjacent cortical areas), unlike those in more distant areas of neocortex, persist beyond the period of short-term memory and can withstand significant interference. Since these representations encode specific stimulus characteristics, they could be used to mediate a perceptual matching of characteristics of previous and current stimuli. This conclusion is consistent with our proposal that the parahippocampal region supports intermediate-term recognition of specific items in DNMS and in object discrimination learning – tasks for which performance is severely impaired after parahippocampal damage.

5.3. Hippocampal processing of comparisons among events

Studies on both monkeys (Riches et al. 1991) and rats (Sakurai 1990a; 1990b) indicate that, in contrast to both neocortex and parahippocampal areas, hippocampal cells do not actively fire throughout memory delays in response to previously presented sample stimuli, nor do they demonstrate passive representations in the form of diminished stimulus-specific responses. Some studies have reported delay related hippocampal cellular activity, but the pattern of their activation is not consistent with the maintenance of an active perceptual representation (Otto & Eichenbaum 1992b; Rolls et al. 1989a; Watanabe & Niki 1985); such activity, when it does occur, probably reflects unidentified behavioral events that occur during the delay period. For example, Watanabe and Niki (1985) described cells that fired consistently at specific periods during a portion of the memory delay, but no cells demonstrated stimulus-elicited responses that were sustained throughout the delay, as should be expected of an actively maintained stimulus representation. Furthermore, Riches et al. (1991; see Brown et al. 1987) contrasted the stimulus-specific response decrements observed for visual stimuli in the parahippocampal and inferotemporal regions with the absence of such responses in any hippocampal area. A recent report by Rolls et al. (1993) confirms and extends this finding. They found that hippocampal cells showed diminished responses to repeated visual cues presented with varying numbers of intervening items in a serial recognition task; these responses persisted across several intervening items but were observed for all familiar stimuli. In one study it was reported that hippocampal cells maintained passive memory representations for the location of a cue within scenes (Rolls et al. 1989b), this is consistent with our view that the hippocampus itself may play a role in intermediate-term storage for relational representations (see sect. 4.8).

The absence of lasting representations for single stimuli in hippocampal neurons has led Brown et al. (1987) to question whether the hippocampus is involved in memory storage. Indeed, by this criterion, their point is well taken. There is now compelling neurophysiological evidence, however, indicating that the hippocampus itself does indeed play a role in recognition memory, albeit one that does not include the storage of encodings for single specific items. Instead, it appears that hippocampal cellular activity at the time of recognition reflects judgments derived from comparisons between the sample and match cues, and that this matching process may contribute to recognition performance. For example, during stimulus sampling in DNMS tasks, hippocampal neurons in both rats (Figure 4c; Otto & Eichenbaum 1992b; Sakurai, 1990b) and monkeys (Riches et al. 1991) respond differentially to the match and nonmatch relationship between stimuli, and do so on all trials *independent of the particular sensory stimuli that compose the stimulus comparisons.* Thus, the hippocampal representation does not reflect the perceptual qualities of particular stimuli but, rather, the abstraction of relevant relations among those stimuli. In other words, during recognition memory

tasks, the responses of hippocampal cells depend on both previous and current stimuli, but their firing reflects only the *outcome* of the match or nonmatch judgment. We take such a neural correlate of abstract relationships as precisely the kind of representation that would be expected to support a relational memory organization. Relating these findings to descriptions of the relatively limited effects of selective hippocampal formation or fornix lesions on DNMS performance, it appears that this kind of processing may contribute to, but is not ultimately critical for, intermediate-term recognition memory. In addition, even in discrimination tasks where comparison of current stimuli to recently presented cues is not explicitly required, hippocampal neuronal activity reflects the processing of such comparisons (Eichenbaum et al. 1986b; Foster et al. 1986). These findings confirm the similarity of hippocampal involvement in DNMS and discrimination learning described above.

Our characterization of hippocampal cellular activity as reflecting abstractions of the relations among cues is consistent with the observation that hippocampal cellular activity is associated with both an animal's position within an environment (O'Keefe 1976) and spatial relationships among environmental cues and critical discriminative stimuli (Wible et al. 1986; Wiener et al. 1989; for review see Eichenbaum & Cohen 1988). Spatial representations ("place fields") of hippocampal neurons do not depend on the immediate presence of any particular cue, and can sustain subtle alterations of the environment or removal of one of several spatial cues (Hill & Best 1981; O'Keefe & Conway 1978). Furthermore, these spatial representations can be highly selective to particular environments (Thompson & Best 1989), and spatial codings are unrelated across different environments, and different behavioral paradigms performed in the same environment (Cahusac et al. 1989; Wiener et al. 1989). Environmental alterations that change the rat's judgment about the overall individuality of the environment result in dramatic and unpredictable effects on the hippocampal spatial representation (Bostock et al. 1991; Breese et al. 1989; Muller & Kubie 1987). For example, after a stable spatial representation was observed in an environment, a subtle stimulus change at first produced no alteration in the spatial representation, but after multiple comparisons between the original and changed environment were permitted, a new and unpredictable spatial representation appeared for the changed environment (Bostock et al. 1991). Conversely, even when all the cues that ordinarily determine spatial orientation are removed, hippocampal place representations persist in correspondence with the animal's judgment of its location, as reflected by behavioral choices (O'Keefe & Speakman 1987; see also Muller et al. 1987; Quirk et al. 1990). Each of these findings is consistent with our conclusion that hippocampal processing does not involve sensory-specific codings, but rather reflects the outcome of relational judgements in terms of abstract, and in these cases, spatial, relations in current or past experience. Finally, this integration of the findings on place cells with our conception of relational processing by the hippocampus is consistent with our notion that the critical role of the hippocampus in spatial memory is a strong example of its more general role in memory organizations.

Finally, although there is little data that directly bears on this question, it is appropriate to ask how hippocampal representations of abstract relations can influence or mediate the storage of stimulus-specific representations in parahippocampal and cortical areas. Of particular relevance are recent findings of Miyashita et al. (1992), suggesting that neurons at the border of the parahippocampal region and temporal association cortex represent long-term relational representations. The firing patterns of these cells reflected reliable repetitive sequences of visual stimuli presented in a recognition memory task and assigned relations among stimuli presented in a visual paired-associate task. Although it has not been demonstrated that these neural correlates were dependent on hippocampal function, the learning of sensory paired-associates has been shown to be sensitive to damage in the parahippocampal region (Bunsey & Eichenbaum 1993a). Thus, it may be that processing within the hippocampal system mediates a permanent cortical organization of perceptual and other cortical representations.

6. Combining the anatomical, behavioral, and neurophysiological findings in a model of memory processing by the cortex and hippocampal system

Evidence from several sources converges on a set of characteristics for each stage of the model presented in Figure 1. Both the neuropsychological findings on amnesia and the behavioral physiology of the hippocampal system serve to dissociate the temporal and representational properties or components of hippocampal system-dependent memory processing, consistent with our view that these properties should be thought of as orthogonal dimensions. The anatomical bases of this dissociation suggest that specific hippocampal areas contributing to declarative memory have different processing functions. The behavioral physiology of neocortical and hippocampal structures complements the neuropsychological findings and clarifies the respective roles of specific components of this system.

The characteristics of these components are outlined in the following model for successive stages of memory processing. Prior to processing by the hippocampal system, neocortical areas create specific perceptual representations that can be sustained briefly. These representations are very sensitive to interference from intervening perceptual processing which probably results in new neural activity patterns that supplant such active memory representations. Neocortical areas are also capable of passively maintaining memory traces in a form that may persist as long as the level of intervening interference is low. Such memory traces are seen to support perceptual matchings between current and stored representations and can support performance in short-term recognition and priming, consistent with the observed sparing of short-term memory even in severe amnesia.

At the first stage of processing within the hippocampal system, perceptual codings reach the parahippocampal region where functionally distinct representations of the same events converge prior to processing in the hippocampal formation itself. These cortical areas do not hold information by sustaining neural activity but can maintain a passive trace that persists through considerable inter-

ference and intervening processing. A matching between the intermediate-term store in the parahippocampal region and current representations in neocortex could mediate retention in recognition memory paradigms, accounting for the finding that parahippocampal areas may be sufficient to support DNMS performance in the absence of normal hippocampal function. However, in our view, the representation in the parahippocampal region does not constitute a full relational coding, and therefore would not be expected to be sufficient, even during intermediate periods, for tasks in which a relational representation or its flexible expression is required.

At the second stage of hippocampal processing, the hippocampal formation does not maintain a memory representation of single sensory cues, but instead processes comparisons between current stimuli and representations of previous stimuli, presumably those maintained at earlier levels of this system. Hippocampal processing appears to be quite different from the perceptual matching taking place in cortical areas. Thus, hippocampal processing relies on cortical inputs (V. M. Miller & Best 1980) and presumably exerts its effects by modifying those inputs or making connections among those cortical areas (e.g., Halgren 1984; Miyashita et al. 1992; Squire et al. 1984). In recognition memory, the hippocampus processes comparisons between current and previous stimuli, as well as rich episodic and contextual information that goes beyond the strict perceptual properties on which cortical matchings are based; this may in some cases make a distinctive contribution to intermediate-term memory.

When the requirements of a task go beyond what can be accomplished by sensory matching processes, requiring comparisons among experiences with items and the flexible expression of memories, the entire hippocampal system contributes to a distinctly new capacity for declarative memory representation. Orthogonal operations drawing on the persistence of individual representations and organizing these items according to important relationships among them are differentially supported by, and interact at, separate processing stages. Specifically, the persistent individual representations stored in the parahippocampal region are exploited and then elaborated by relational processing in the hippocampus itself. As the full extent of interactions between intermediate-term storage and relational processing proceeds, the overall memory organization is modified by, and benefits from, the information newly added to its structure. We propose that these interactions, by feeding back and forth, can go on for a significant period, and may be reinstated repeatedly by experiences that bear partial similarity to the learning event. This repetitive processing could contribute to the "consolidation" of memories for very long periods.

7. Comparisons of the present model to theories of hippocampal function

The goal of the present review has been to show that there are two distinct properties whereby hippocampal system-dependent memory differs from hippocampal system-*in*dependent memory and to propose that these are mediated by functionally distinct component processes of the hippocampal system. Several previous accounts, including our own, have focused on either the temporal or the representational properties of hippocampal system function. In addition, several models of hippocampal-cortical interactions that resemble the current view have been proposed.

7.1. Accounts that focus on the temporal distinction

Among prominent proposals of this category are the original account of hippocampal function as mediating the consolidation of memories (Scoville & Milner, 1957) and the more recent proposal that the hippocampus acts as a temporary buffer for intermediate-term storage (Rawlins 1985). These views have certainly captured the essence of our proposal with regard to the temporal properties of hippocampal processing, and our description of the role of the parahippocampal region in intermediate-term storage borrows heavily from Rawlins' formation of this distinction. His particular proposal also requires more detailed consideration here because it specifies how the temporal and representational properties of hippocampal processing interact. Central to Rawlins's view was that the hippocampus acts as a high-capacity, intermediate-term buffer, as distinguished from hippocampal system-independent systems that can support learning that involves less information and fewer associations over brief delays, as is customary in simple conditioning procedures. His account predicts impairments in animals with hippocampal system damage in any task that has significant delays or exceeds the minimal capacity of extrahippocampal systems. For example, in the radial maze, performance on consistently nonrewarded arms involves virtually no delay between a visit to the arm and its consequence, whereas performance on working memory arms requires memory bridging a long delay between a rewarded visit and later decisions about whether to visit that arm. Correspondingly, animals with hippocampal system damage perform well on the consistently nonreinforced component and poorly on the working memory component of the task. To the demands of working memory tasks Rawlins's analysis added the dimension of time and the interference associated with intervening arm visits. Similar analyses were applied to performance deficits across a wide range of tasks with significant memory delays.

In accounting for the findings across the full range of behavioral paradigms, two other properties associated with the temporal distinction may need to be considered. First, the period of critical hippocampal system involvement varies across tasks; forgetting rates of animals with hippocampal system damage are highly dependent on the nature of the task (see Winocur 1991, and the discussion of persistence functions in section 3.2; also Figure 3). Second, the degree to which the pattern of performance impairments can be explained simply by the length of the required temporal delay likewise varies; factors of capacity and interference also come into play in situations where impairments are observed at short critical delays. Thus, for some tasks it is not just the delay that matters, but whether there are other behaviors executed during the delay, or multiple items that have to be remembered, as in list learning, radial maze working memory, and spatial memory. The increased susceptibility to inter-

ference in animals with hippocampal damage has been highlighted in other accounts (Jarrard 1975; Squire & Zola-Morgan 1991; Winocur 1985; for a detailed discussion see Shapiro & Olton 1994). Different forms of interference can act either to require a greater memory capacity in tasks where multiple items are not in direct conflict, as in list learning or concurrent discrimination, or to increase the demand for relational processing when the items are ambiguous, as in working memory and spatial tasks. From the present account it is predicted that the parahippocampal area, but not the hippocampal formation, will be critical to the first form of interference described above and that both areas will be critical to the second. However, as Shapiro and Olton (1994) have warned, parametric issues such as the ordering of items in concurrent discrimination can influence which type of interference is invoked. These considerations emphasize the need to clarify the consequences of different types of interference – components of the hippocampal system may subserve different roles in interference reduction. One of these may be based on a high-capacity intermediate-term storage mechanism in the parahippocampal areas and another on hippocampal system-dependent relational processing that separates and organizes potentially contradictory information (see Shapiro & Olton 1994).

The temporal properties of hippocampal memory processing must be considered for a full understanding of the neuropsychological findings (Cohen & Eichenbaum 1993; see also discussion of Rawlins 1985), but neither the consolidation account nor the temporary buffer account can explain the full range of impairment and sparing following hippocampal damage, nor can these accounts encompass the full range of physiological data presented here. Instead, the relational processing properties of the hippocampal system must also be incorporated into any account.

7.2. *Accounts that focus on the representational distinction*

Other accounts from the animal literature have focused on the representational properties of hippocampal function, and although they would seem to have little in common and to make no contact with the literature on human amnesia, taken together they converge on a view in which the hippocampal system mediates critical relations among perceptually distinct cues that make up spatial maps, contexts, stimulus configurations, or conditional operations. Furthermore, implicit in the design of tasks that assess these types of learning are requirements for flexible expression of memories across situations where individual cues are ambiguous. Such tasks emphasize the relational character and representational flexibility that we deem critical to declarative memory. Conversely, each of these accounts distinguishes some form of relational representation from a hippocampal system-independent capacity for learning the significance of individual cues. A brief review of these theoretical positions will reinforce this point.

One prominent account focuses on the distinction between a hippocampal system-dependent capacity for "cognitive mapping" and a hippocampal system-independent capacity for "taxon" learning (O'Keefe & Nadel 1978). The spatial processing that underlies cognitive mapping is a superb example of how we envision the hippocampal formulation to participate in the creation of a memory organization, in this case for the geometric organization of the environment, and how a relational organization supports flexible memory expression, in this case for navigation through a learned environment. Conversely, taxon learning quite clearly captures the properties central to the acquisition of biases to individual stimuli. Indeed, the cognitive mapping view is completely compatible with our proposal regarding relational representation except insofar as it limits its scope to geographic relations, ignoring the wide range of nonspatial and temporal relations for which we have argued the hippocampal system is also critical.

Other accounts capture different aspects or examples of relational representation. Olton et al.'s (1979) distinction between a hippocampal system-dependent capacity for working memory and a hippocampal system-independent capacity for "reference memory" focuses on the organization and flexibility required when performance depends on a representation of a sequence of behavioral episodes. Gray's (1982) model of the hippocampus as a comparator of current information and stored predictions offers a set of mechanisms by which working memory functions may be accomplished (see also Gabriel et al. 1980).

In addition, multiple accounts have been proposed to explain the phenomena of conditional and contextual learning, each with a different perspective on relational processing. These include proposals that have distinguished the hippocampus's role in learning in terms of "contextual encoding" versus "learning along the performance line" (Hirsh 1974), learning of "external context attributes" versus acquiring "rules" (Kesner 1984), "configural association" versus "simple association" (Sutherland & Rudy 1989), and memory for the spatial configuration of items in "scenes" versus distinct places (Gaffan & Harrison 1989). Each of these proposals captures the aspect of hippocampal processing leading to the disambiguation of cues as their predictive value varies under different circumstances. However, one of these models is, we believe, incorrect. The hippocampal system (or at least the hippocampal formation) does not seem to be required for learning compound or "configural" cues *per se*, as was suggested by Sutherland and Rudy (1989), but is required for configurations of cues when the information must be encoded in terms of relations among perceptually independent items.

What is critical to take from this list of proposals is that each of them, though limited in scope to one domain of behavioral paradigms, is characterized by the properties of relational processing and representational flexibility outlined above. The characterization of hippocampal processing that we have offered finds a common thread that runs through all these proposals (see Cohen & Eichenbaum 1993 for a review of these theories contrasted to our own). None that focuses on the representational distinction has fully incorporated the findings on the delay-dependent parameters of forgetting, described above. (The one account that has explicitly attempted to combine the temporal and representational properties proposed a temporal buffer for comparator operations of the hippocampal system; Gray & Rawlins 1986.)

7.3. Accounts that focus on cortical-hippocampal interactions

Several other accounts have offered mechanisms for interactions between the cortex and hippocampal system. Avoiding a strict memory interpretation, Gray (1982) suggested that the hippocampus compares current information with cortical records of previous predictions and consequently selects an appropriate behavioral mode for action. Other theorists, focusing on a memory interpretation, have suggested that the hippocampal system coordinates the consolidation of memories in the cortex. These accounts vary in the mechanisms by which this coordination is accomplished and the purpose of the cortical-hippocampal interactions. Squire et al. (1984) proposed that the hippocampal system optimizes the coherence between cortical areas responsible for encoding different aspects or elements of events. Teyler and Discenna (1986) suggested that such a process can be accomplished by the hippocampus using a long-term potentiation (LTP) mechanism to temporarily maintain indices for the widespread cortical areas being coordinated. Wickelgren (1979) suggested that the hippocampus could act to bind separate cortical representations by a process he referred to as "chunking"; Halgren (1984) specified how hippocampal LTP could mediate such a process and subserve the recovery of memories from partial information. McNaughton and Morris (1987) and Rolls (1989) have described computational models of how such processing could separate cortical associations that might otherwise be confused; Worden's (1992) model suggests mechanisms by which the hippocampus can fit "fragments" of space into a cognitive map. Each of these accounts offers an interesting proposal for the role of the hippocampal system in mediating eventual permanent cortical storage (see also Miller 1991 for review). However, in contrast to the present proposal, each combines the intermediate-term storage and representational processes of the hippocampal system. The present proposal offers a distinct departure from the common view that the temporal distinction is merely an aspect of the representational function of the hippocampal system, and it leads to testable experimental predictions that could elucidate the anatomical and physiological bases of these two distinctions of hippocampal memory processing.

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Is Eichenbaum et al.'s proposal testable and how extensive is the hippocampal memory system?

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A reassessment of the relative functions of medial temporal lobe structures in memory is clearly needed, and Eichenbaum et al. are to be congratulated for their contribution to this debate. They have provided a very useful working hypothesis. On a minor note, it is perhaps unfortunate that the word "hippocampus" was not removed from the title of the medial temporal memory system as its presence not only leads to some ambiguity, but also reinforces earlier notions about the preeminence of this structure. Much more important, the value of Eichenbaum et al.'s model will depend on (1) whether it has predictive value, and (2) whether it can be integrated into what is known about other brain regions involved in memory.

Is it predictive? Some aspects of Eichenbaum et al.'s proposals can readily be tested. For example, it should not be possible when testing memory to produce a double dissociation between the effects of lesions to the "hippocampal formation" and the "parahippocampal region." A report that neurotoxic lesions in the entorhinal and rhinal region in rats can spare tasks known to be disrupted by hippocampal damage (Hagan et al. 1992) casts some doubt on this prediction, but it will be necessary to await the outcome of studies using lesions more precisely conforming to the regions described by Eichenbaum et al.

It will prove more difficult to test other aspects of the proposal, however. One aspect is that the hippocampal formation is required for "relational representations." Although this term may capture some important component of hippocampal activity, its imprecision makes it difficult to predict in advance those tasks reliant on hippocampal function. Furthermore, it is hard to conceive of a learning task where some sort of relational process could not be invoked (e.g., compositional relations or temporal relations). Taking working memory as an example, Eichenbaum et al. argue that this form of "episodic" memory requires relational representations. Nevertheless, hippocampal or fornix lesions sometimes have no effect on tests of nonspatial working memory, even when there are heavy demands on distinguishing between familiar stimuli (Aggleton et al. 1986; Correll & Scoville 1965b; Shaw & Aggleton 1993). Although it is possible that the tasks used in these particular experiments lacked a relational component, it is difficult to see how this could have been predicted in advance.

Can it be integrated? A central feature of Eichenbaum et al.'s proposal is the functional division of the "hippocampal system" into a "hippocampal formation" and a "parahippocampal region." The inclusion of the fornix in the hippocampal formation makes considerable sense in the light of evidence that earlier discrepancies between the effects of fornical and hippocampal lesions were due to inadvertent parahippocampal damage made during the course of medial temporal surgeries (Gaffan & Lim 1991). Thus hippocampal lesions which spare rhinal tissue not only lead to less severe memory deficits than previously reported, they also more closely resemble the effects of fornix transection (Aggleton et al. 1992; Zola-Morgan & Squire 1993).

The inclusion of the fornix in the "hippocampal formation" does, however, raise a number of important implications. The current model describes a system for the processing and storage of declarative memories in which the flow of information is contained within the temporal lobe. Yet it is known that damage to the medial diencephalon can produce a loss of declarative memory ("diencephalic amnesia") similar to that found after medial temporal lobe damage. If double dissociations between temporal lobe and diencephalic amnesia were readily available then it could be argued that these amnesias reflect disruptions to quite different aspects of memory. In fact, such dissociations are not forthcoming. Furthermore, the fornix provides a direct route by which the hippocampus projects to several medial diencephalic regions implicated in diencephalic amnesia, most notably the mamillary bodies and the anterior thalamic nuclei (Aggleton & Sahgal 1993; Dusoir et al. 1990). Consistent with this is evidence from lesion studies in rats which suggests that fornical *output* connections to medial diencephalic sites, such as the anterior thalamic nuclei, are vital for certain memory tasks, such as delayed nonmatching-to-position (Aggleton & Sahgal 1993). Thus, the effects of fornix transection are not simply due to the loss of some modulatory input to the hippocampus, from the medial septum, for example. It would appear, therefore, that the hippocampal mnemonic system is more extensive than that described in the target article.

The full extent of this "system" then depends on the route of the critical diencephalic outputs (i.e., the outputs from those regions receiving hippocampal projections) and the extent of information flow within this route (as distinct from some form of "enabling" process). One quite plausible option is that the critical outputs from the diencephalon are those that project back to the "hippocampal system." Clearly, if this is so then Eichenbaum et al.'s model is not seriously compromised: all that is required is a "hippocampal-diencephalic loop." If, however, the diencephalic contribution depends on the output of information to other sites (e.g., prefrontal cortex), then the present model is seriously weakened. Unfortunately, the critical outputs from the medial diencephalon have yet to be defined, so this issue remains to be resolved. Nevertheless, the relationship between temporal lobe and diencephalic structures is one that cannot be ignored when considering the implications of this model and, hence, the extent of the "hippocampal system."

Remembering spatial cognition as a hippocampal functional component

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Eichenbaum, Otto & Cohen have admirably proposed an important model that explains a vast body of often inconsistent experimental findings that have been used to understand the role of the hippocampal formation (HF) in cognition. They have succeeded in arguing coherently that to try to understand hippocampal function within the framework of a single cognitive process is unrealistic, and they demonstrate convincingly that HF has at least two distinct memory functions. However, I feel that their target article fails to convey the unique importance of HF for relational (representational) processing of spatial information.

The authors view spatial information processing as one example of a more general type of relational processing carried out by HF. They argue that in some spatial contexts HF lesions impair learning while in others they do not. The same pattern can be found with nonspatial experimental paradigms. What they fail to point out is that examples of spared and impaired spatial learning following HF lesions (Eichenbaum et al. 1990; O'Keefe & Conway 1980) are entirely consistent and predicted by the cognitive mapping model of O'Keefe and Nadel (1978). As an additional example, experiments on homing pigeons also demonstrated spared spatial learning when an associative strategy could be used as predicted by the cognitive map model (Bingman et al. 1988). In contrast, I am aware of no model that would have predicted the pattern of impairments and sparing following HF lesions across the nonspatial tasks described. For example, it is only by examining post hoc the details of the experimental procedures that one can explain why Sutherland and Rudy (1989) found an apparent deficit in a conditional learning task following HF lesion while Davidson et al. (1993) did not. Although the general relational learning model developed by Eichenbaum et al. can successfully explain existing findings on nonspatial learning, it is not clear to me that it would adequately predict outcomes of future experiments examining the relationship between HF and nonspatial learning. The ease with which one can predict the effects of HF lesions on spatial tasks compared to nonspatial tasks would suggest that there is indeed something special about space.

Electrophysiological findings can be used to make the same point. Eichenbaum et al. examine a number of recent studies that have looked at nonspatial hippocampal cell firing (e.g., Rolls et al. 1993) to emphasize the role of HF in general relational memory organization. However, they made little effort to relate the vast literature on HF place cells (Muller et al. 1987) and the developing literature on HF direction-sensitive cells (Taube et al. 1990) to relational memory organization. This is surprising because it seems relatively easy to conceptualize how HF place cells and direction-sensitive cells could collectively operate to regulate spatial relational representations. In contrast, it seems more difficult to understand, for example, how diminished responses that generalize across familiar visual cues (Rolls et al. 1993) relate to general relational processing. The electrophysiological data also emphasize the special relationship between HF and space.

The literature on avian HF offers perhaps even more compelling reasons to believe that spatial processing should be treated as a distinct system. HF volume is relatively larger in a wide variety of species that store and later recover food compared to related species that do not (e.g., Krebs et al. 1989). This finding is thought to reflect the action of natural selection operating on HF to enhance some aspect of spatial information processing associated with relocating stored food. Indeed, the larger HF does seem to confer a spatial information processing advantage. It has been reported that in an operant spatial nonmatching task, one species of jay that stores extensively and has a large HF outperformed another species that stores less (Olson 1991). What is truly remarkable, however, is that when the task was changed to a nonspatial nonmatching task the between-species performance difference disappeared (A. Kamil, personal communication). Assuming that both spatial and nonspatial nonmatching involves HF relational processing, the bird results raise the real possibility that HF spatial processing can be dissociated from nonspatial processing because natural selection can act upon it independently. Alternatively, Eichenbaum et al. could legitimately argue that only spatial nonmatching involves relational processing whereas nonspatial nonmatching involves only the temporary maintenance of perceptual memory. In this case, it would be general relational processing capacity that was influenced by natural selection. In any event, the jay results imply that natural selection can act independently on distinct cognitive processing systems probably regulated by HF.

There is also some neurochemical evidence from rats to suggest that more than one relational processing system may involve HF and that they are in some way dissociable. A variety of N-methyl-D-aspartate (NMDA) receptor antagonists have been shown to disrupt spatial learning in a water maze (Morris et al. 1986), but not to disrupt radial maze working memory in a manner similar to hippocampal lesions (Bolhuis & Reid 1992).

Although these studies do not specifically look at HF, they do suggest the possibility that HF NMDA receptor activation is necessary for relational learning in the water maze but not the relational learning that supports working memory. Yet it is not clear how this may relate to the possible separation of spatial and nonspatial processing.

In summary, the model proposed by Eichenbaum et al. offers a major conceptual breakthrough by proposing that HF regulates two independent cognitive processing systems. However, they may not have gone far enough. It seems that spatial relational processing must be viewed as having a unique relationship with HF (Bingman 1992). It is possible, albeit unlikely, that HF regulates a third cognitive system dedicated to space. For animals, however, it seems more reasonable to assume that HF relational processing is essentially spatial. Nonspatial relational processing deficits found in animals following HF lesions would be a consequence of disrupting cognitive processes that natural selection has shaped specifically for spatial information. Nonspatial deficits occur because unnatural laboratory tasks – tasks that have little in common with the type of learning situations that shaped HF evolution – require the type of relational processing designed for space.

The hippocampal system, time, and memory representations

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Studies on the role of the hippocampus and associated structures in learning and memory have generated a complex set of findings. The enterprise has been bedevilled by issues of cross-species comparison, the nature and extent of lesions used, and the types of tasks used in behavioural assessment. Many theories have been developed in an effort to make sense of the wide variety of empirical findings. Nevertheless, few would disagree that the role of the hippocampus is as yet inadequately characterised. Eichenbaum and colleagues have made a laudable attempt to integrate a bewildering array of findings into a conceptual whole. The potential strength of their proposal is twofold: they (1) combine two important suggestions about the function of the hippocampal system, and (2) specify this system to include a number of extrahippocampal structures. In doing so, their theory works hard to reconcile discrepant findings. However, the apparent strength of their theory is actually its Achilles' heel. Their theoretical framework is dangerously circular and their concept of relational representation so loosely specified that existing competing data sets can only be harmonised superficially.

An important aspect of the present theory is the distinction between individual and relational representations. We find the definition of these two concepts (sect. 4.1) extremely vague. It is unclear what psychological phenomena form the basis of this distinction. For example, one might ask which kind of representation is involved in Pavlovian conditioning. As the hippocampus is supposed to be involved in relational representations and ibotenic acid lesions to the hippocampus do not affect Pavlovian conditioning or latent inhibition (Honey & Good 1993), presumably this implies that these forms of learning involve individual representations only. This would seem an atypical way of characterising associative learning. Furthermore, in studies of perceptual learning, it has been demonstrated that representations formed during Pavlovian conditioning can be used in novel situations, which is not consistent with the definition of "individual representations." Similarly, it would appear that the only criterion for distinguishing whether an animal is using "relations among perceptually independent items" or "compound or 'configural' cues per se" (sect. 7.2, para. 4) is sensitivity to hippocampal damage – an argument which is inherently circular. Finally, Murray et al. (1993) recently showed that lesions restricted to the hippocampus do not affect stimulus-stimulus (S-S) learning in monkeys, but rhinal cortical lesions do. Does this then mean that S-S learning involves individual representations, or that the rhinal cortex is involved in relational representations?

In section 3.1, Eichenbaum et al. suggest that temporarily graded retrograde amnesia (RA) after damage to the hippocampal system has been demonstrated in a number of animal studies. It is not clear how this evidence fits with the present theory. Do demonstrations of such gradients in RA bear upon the authors' suggestion that the parahippocampal region, and not the hippocampus, is involved in intermediate-term memory storage? Or do they support the suggestion that "the entire hippocampal system" is involved in the intermediate storage of "more complex information?" (sect. 3.1, last para.). Two important issues here are that, first, gradients in RA have not consistently been demonstrated in animal studies involving lesions to the hippocampal system, and, second, studies demonstrating such gradients showed a great deal of variation as to which elements of the hippocampal system were lesioned (e.g., Bolhuis & Steward 1993; Bolhuis et al. 1994; Kim & Fanselow 1992; Salmon et al. 1987, Sutherland & Arnold 1987; Winocur 1990, Zola-Morgan & Squire 1990). Gaffan (1993) recently concluded that there was no gradient in RA for discriminations of complex naturalistic scenes after fornix transections. Gaffan proposes alternative explanations for apparent RA gradients in animals and man. Thus, from all these studies taken together it is not clear whether there is a gradient of RA after lesions to the hippocampal system (see Bolhuis et al. 1994; Gaffan 1993, for reviews), and indeed which part of this system would be involved.

Reid et al. (1991) reported that ibotenate hippocampal lesions do not affect simultaneous olfactory discrimination learning, in contrast to Eichenbaum et al.'s finding of marked impairment on a formally identical task after fornix lesions. Eichenbaum et al. might wish to dismiss this contradiction by suggesting that, as Reid et al.'s apparatus differs in detail from theirs, a different form of learning (presumably nonrelational) is encouraged. Within their own body of experimental work, fornix lesions have been found to have, on one occasion, no effect on successive go/no-go olfactory discrimination learning (Eichenbaum et al. 1986a), and yet on another occasion a facilitatory effect (Eichenbaum et al. 1988). This discrepancy arose despite the use of identical apparatus, odour problems, rat strain, and lesions. Within the framework of the present theory, are we invited to conclude that some procedural difference between the two experiments (undetected by the authors) was at play in biasing the subjects towards different types of learning, differentially susceptible to fornix damage? Further theoretical and methodological issues concerning olfactory learning studies have been debated elsewhere (Reid & Morris 1993).

Recording the recognition due to the parahippocampal region places hippocampal relational encoding in context

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Recent years have seen the increasing fractionation of mnemonic processes together with the increasing realisation that the brain contains a number of memory systems that may in part

overlap in their function. In this target article, Eichenbaum et al. suggest further steps in this dissection of memory.

Theories of hippocampal function are confronted with two questions to which there is as yet no generally agreed-upon answer: (1) what does the system do, and (2) for how long does it do it? The chief difference between previous theories of hippocampal function and that of Eichenbaum et al. is that their theory attempts to address both these issues and in so doing gives a distinctive role to the parahippocampal region.

The suggested division of the cortex into three regions – neocortical, parahippocampal, and hippocampal – each with particular memory functions, is an important advance (see also Brown 1990). However, there are already indications that the division between the "neocortical association areas" and the "parahippocampal region" will not be easy to determine precisely, and that the parahippocampal region is itself more than one functional area. Thus, on the one hand, neurones that respond differently when a visual stimulus is shown for a second time (i.e., show "recognition-related" activity) are found within the "parahippocampal region" in the perirhinal and temporal polar cortex, but have *not* so far been found in areas TF or TH of the parahippocampal gyrus (Brown et al. 1987; Riches et al. 1991). On the other hand, such neurones also extend into more lateral parts of the inferior temporal cortex outside the "parahippocampal region," some having memory spans of at least a few minutes (Fahy et al. 1993).

Experiments on the neural basis of visual recognition memory provide further insights concerning the proposed division of function between the three cortical regions. Two types of information that may be of importance for the successful performance of recognition memory tasks are the familiarity of material (how often or for how long it has been encountered previously) and how long ago it was last encountered (recency). Many working memory and delayed matching or nonmatching-to-sample tasks can be accomplished using recency or familiarity judgements (Brown 1990; Fahy et al. 1993). Human subjects can distinguish these types of information: for example, we know whether something is familiar as well as whether we have seen it recently. Neurones in the perirhinal and temporal polar cortex demonstrate the separable encoding of recency and familiarity information (Fahy et al. 1993). Thus, in agreement with Eichenbaum et al., it seems that information concerning the prior occurrence of individual items is available in at least part of the parahippocampal region. However, neurones of this region demonstrate "memory spans" that last more than just a few minutes, that is, longer than is required by the "intermediate memory" proposed for the parahippocampal area. Indeed, certain neurones in the region evidence access to information held in memory for 24 hours or more (Fahy et al. 1993). Nevertheless, in further agreement with Eichenbaum et al., such neurones are comparatively rare in the hippocampal formation (Brown et al. 1987; Riches et al. 1991). Moreover, the mnemonic capabilities of neurones in perirhinal and temporal polar cortex are more impressive than those so far reported for neurones in the hippocampal formation (Fahy et al. 1993; Miller et al. 1993; Riches et al. 1991; Rolls et al. 1993), suggesting that these capabilities do not depend on hippocampal function.

One type of information signalled by neurones of the hippocampal formation signal is contextual, particularly but not exclusively spatial (e.g., Brown 1982; O'Keefe & Nadel 1978). Many recognition memory tasks require knowledge of the context of occurrence of material. For example, such knowledge is needed when a subject is asked to recognise a word from a previously presented list if both the target and distractor words have been encountered many times previously so that recency and familiarity discrimination are difficult (e.g., Brown & Brown 1990). The subject must then remember the event (context) within which the target word was encountered. An important distinction here is that the "context" requires relational processing (in Eichenbaum et al.'s terminology) of many stimuli and cannot be provided merely by a simple association of the target item with a single stimulus (the neocortex is probably adequate for such simple associations).

There is a growing consensus that the hippocampal formation is crucial to event (episodic) memory and that its function is conserved across species along with its anatomy. Eichenbaum et al. provide a valuable review of some of the evidence for this belief. I would like to make plain my agreement with this opinion, in view of their attributed comment in section 5.3, para. 2. Our 1987 article (Brown et al. 1987) says only that the inferomedial temporal cortex may be more important than the hippocampus for certain types of mnemonic information (i.e., recency and familiarity). In another article (Brown 1990, pp. 235–6) I have written,

> Memory for events displays two distinctive features. First, learning can occur as a result of a single trial. . . . Second that events . . . can be extremely varied and disparate. . . . At the time of occurrence of the event itself the fact that all the features are experienced co-temporaneously solves the problem of their association. However, subsequent recollection of the event can be possible only if the fact of their occurrence together is stored in the brain. . . . Thus, a modifiable neuroanatomical pathway has to exist between each particular neural representation and every other such representation. Efficient implementation of this requirement is likely to place important anatomical constraints upon the system. . . . The cytoarchitecture of the hippocampal formation, in contradistinction to that of the neocortex, suggests that the hippocampal formation could provide the necessary hardware for the formation of associational connections between subsets of many, varied neuronal representations, as is required for event memory.

Thus my view, like that of Eichenbaum et al., is that the hippocampal formation solves the severe "binding problem" that arises as a result of different types of information being processed in widely separated regions of the cortex. Eichenbaum et al. do not attempt to explain *how* the hippocampal formation solves this problem; analysis of how such a problem can be solved should lead to a much better understanding of exactly what the hippocampal formation does. In addition, details concerning the output of the system are critical to this understanding. Unfortunately, the functional operation of both the subcortical (fimbria/fornix) and cortical (parahippocampal) outputs are as yet little understood.

A critical issue is to determine whether the hippocampal formation itself stores information or merely facilitates its storage elsewhere; in other words, in this case, is relational information stored in the hippocampus? If the hippocampal formation does store information, there is a widespread, though not universal (e.g., O'Keefe & Nadel 1978) view that the storage is not long-term. The idea that the hippocampal formation might serve as a temporary memory has a long history (see e.g., Douglas 1967; Marr 1971; Rawlins 1985). There is little consensus, however, concerning the length of time for which the hippocampal formation might store information, or what conditions might result in information being transferred out of it. Eichenbaum et al. are also circumspect about these matters, perhaps wisely, because much of the evidence is equivocal. Take, for example, data concerning retrograde amnesia from human amnesic patients. Tests of memory for material encountered prior to the onset of the amnesia typically differ from those administered after its onset. In particular, in tests of memory for material acquired prior to the amnesia the material is likely to have been encountered on multiple occasions and does not necessarily represent discrete events in the patient's life; this contrasts with material presented in tests subsequent to the amnesia's onset. Should sufficient repetition or rehearsal enable the neocortex to learn to solve the test and so become independent of further hippocampal involvement, then damage to the hippocampal system will not affect performance for such material acquired prior to the onset of the amnesia (Brown 1990). Accordingly, such tests do not exclude the possibility that the

hippocampal system is necessary for long-term storage or retrieval in addition to the acquisition of events that are experienced only once. This is only one example of the many remaining uncertainties concerning hippocampal function. By focusing attention on critical issues, Eichenbaum et al.'s review can be expected to assist in the resolution of at least some of the unknowns.

In search of the engrammer

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Clouded by a semblance of heisenbergian uncertainty, the problem of separating process from representation looms large in every corner of neuropsychology. It is as vexing in the old cortex as it is in the new. In both, it is practically impossible to determine whether an amnesia from a lesion is due to the perturbation or a memory processor (a generator, consolidator, integrator, or retriever of memory) or of the neural representation of the engram itself. In the absence of any evidence to the contrary, we adopt in the neocortex the parsimonious position that the two share the same substrate. Electrophysiology tends to bear this out. Neither lesions nor single unit studies yield convincing evidence that the processing and representation of sensory information take place in different areas. All sensory and parasensory areas seem to engage in both perceptual analysis and perceptual memory. To wit, the inferotemporal (IT) cortex is as important for visual processing as it is for visual memory, short-term as well as long-term. Why should it be otherwise? We remember what we perceive and we perceive what we remember – constantly projecting on the world hypotheses and expectations based on memory. This interdependence of the processor and the processed information in either cognitive function – perception and memory – makes it almost obligatory to assume *a priori* that the substrate for both is one and the same. A logical consequence of that assumption is that the microelectrode cannot separate IT areas that discriminate from those that retain – at least for the short-term – colors and shapes (Fuster 1990; Fuster & Jervey 1982). The same seems true for tactile information in parietal cortex (Koch & Fuster 1989; Zhou & Fuster 1992), and for motor or action-related sensory information in prefrontal cortex (Fuster et al. 1982; Quintana & Fuster 1992).

In their target article, Eichenbaum et al. attempt to dissociate representation and processing in the limbic system: representation of "intermediate memory" in the parahippocampal region, relational processing in the hippocampal formation. Their dichotomy is based on an impressive collection of neuropsychological observations from several species. Although the bulk of these observations is fully compatible with their position, it falls short of proving the "orthogonality" of the two functions the authors postulate for the two regions. One would hope that the electrophysiological evidence they adduce in its support would be more convincing than it is. For example, the duration of sustained neocortical cell discharge during active memorization is extremely variable and thus cannot be used as a criterion for defining neuronal memory. Within any given neocortical area, and according to the authors' temporal criteria, some cells would qualify as "brief" and others as "intermediate" memorizers. Hippocampal and parahippocampal neurons have been less explored. Nonetheless, I have found memory cells in CA1 that are indistinguishable from those in IT cortex (Fuster 1991). What is more remarkable is that some hippocampal units seem to discriminate and retain color, hardly a sensory quality associated with hippocampal function. It is true, however, in support of Eichenbaum et al., that in our experience "active memory cells" are less common in hippocampus than in neocortex. It also seems true, from the results of some of the studies they cite, that "passive memory cells," presumably the basis of intermediate memory and consolidation, are more common in the cortex of the parahippocampal gyrus than in the neocortex.

The relational memory-processing function of the hippocampus that the target article postulates is in some respects reminiscent of the role that Rawlins (1985) attributes to the hippocampus. This role could be considered a special case, in the time domain, of the relational role that Eichenbaum et al. postulate for the hippocampus. Neither Rawlins nor these authors, however, seems to have taken note of the fact that their relational role in the time domain is practically identical to the role that this commentator (Fuster 1980; 1985) earlier attributed to the prefrontal cortex. Perhaps we are dealing with the same memory-processing function at different levels of the representational hierarchy. The cross-temporal binding role of the prefrontal cortex would take place at a higher – more cognitive – level, and with broader schemes of memory than that of the hippocampus. Following my reasoning for the identity of processing and representational areas in the neocortex, the time-binding function of the prefrontal cortex derives from its representational function – that is, from the role of this cortex in the representation of temporal gestalts – plans and programs of motor action. Eichenbaum et al. seem to follow similar reasoning for the hippocampus with regard to sensory contents, at least in the initial stages of memory acquisition. An important difference is that, in their scheme of things, the essential elements of the relationship that the hippocampus forms residue in the neocortex. Theirs is as good an argument as present data allow.

A computational perspective on dissociating hippocampal and entorhinal function

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Selective inactivations of hippocampus, subiculum, and entorhinal cortex can have dramatically different behavioral effects (e.g., Jarrard & Davidson 1991; Zola-Morgan et al. 1992). To date, few models or theories have attempted to characterize these differences in function among hippocampal-region structures. The target article by Eichenbaum, Otto & Cohen is a commendable exception, proposing an intermediate-term buffer in entorhinal cortex distinct from representational processing in the hippocampus (including dentate gyrus and subiculum). This hypothesis is similar to one we have recently proposed (Myers et al., submitted). In this commentary, we begin by briefly reviewing our own hypothesis; we then compare it with the ideas presented in the target article.

A computational model of hippocampal-region function. Gluck & Myers (1993) proposed that the hippocampal region is critical for the construction of new stimulus representations during learning. These new representations are biased to differentiate stimuli that predict future reinforcing events and they compress the representations of redundant or cooccurring stimuli. Long-term memory sites in the cerebral and cerebellar cortices are presumed to be unable to form new representations in this way; according to the theory, however, they can acquire the new stimulus representations formed in the hippocampal region. This proposal is broadly consistent with Eichenbaum and colleagues' qualitative characterization of a hippocampal role in forming representations that are sensitive to stimulus relations (Eichenbaum & Buckingham 1990; Eichenbaum et al. 1992a).

We have further suggested that one aspect of our proposed hippocampal-region function may occur in the entorhinal cortex (Myers et al., submitted). In particular, we proposed that entorhinal cortex might perform clustering or compression of multimodal inputs which reliably cooccur. This idea was suggested by the anatomical similarity between superficial entorhinal cortex and piriform cortex (Gluck & Granger 1993), a region which has previously been suggested to perform stimulus-stimulus clustering on olfactory inputs (Ambros-Ingerson et al. 1990; Granger & Lynch 1991; Granger et al. 1989). Hippocampal-region function would then consist of two serial processing stages: redundancy compression in the entorhinal cortex, followed by the differentiation of predictive stimuli in other hippocampal structures. Our hypothesis makes the prediction that behaviors such as latent inhibition and sensory preconditioning, which are interpreted as resulting from redundancy compression, should be eliminated by broad hippocampal-region damage. In contrast, these same behaviors may survive selective hippocampal lesions that do not otherwise damage entorhinal cortex. There are as yet few data explicitly testing this dissociation on classical conditioning tasks, but those few that do exist are consistent with this hypothesis (Myers et al., submitted).

Comparison with Eichenbaum, Otto & Cohen. There is a strong correspondence between Eichenbaum et al.'s characterization of the entorhinal cortex as an intermediate-term buffer and our idea that the entorhinal cortex performs stimulus-stimulus redundancy compression. In particular, one might expect that an intermediate-term memory of the sort proposed in the target article will exhibit generalization or clustering across physically similar cues. Entorhinal representational resources are finite and therefore cannot preserve every piece of afferent information for an indefinite time. One way of reducing the amount of information stored is to generate compressed or clustered representations of cooccurring, and therefore mutually redundant, information. This is consistent with anatomical evidence indicating high convergence of inputs into entorhinal cortex, relative to the number of entorhinal cells available to process this information (Levy 1989).

Although there is considerable theoretical overlap between Eichenbaum et al.'s hypotheses and our own, they are not identical. The primary difference between our hypothesis of entorhinal function and that of the target article is that we have posited active representational recoding processes in the entorhinal cortex, whereas the target article suggests that the entorhinal cortex is a passive store while representational processing occurs in the hippocampus. It would be fairly simple to test this distinction by comparing the effects of selective hippocampal versus entorhinal lesions on tasks that require representational compression but not buffering. As one example, our hypothesis predicts that sensory preconditioning (Thompson 1972) may survive selective hippocampal lesions but not entorhinal lesions. Because sensory preconditioning does not appear to require intermediate-term buffering, Eichenbaum et al. would make the opposite prediction, namely, that sensory preconditioning should depend critically on representational processes in the hippocampus.

A second difference between these two hypotheses is that Eichenbaum et al. assume a functional and anatomical distinction between representational and temporal aspects of hippocampal function. Our own assumption has been that temporal information is instead simply one aspect of stimulus representation, and this is supported by experiments in which the addition of recurrent connections to simple connectionist models allows them to mediate temporal as well as representational aspects of hippocampal system-dependent phenomena (Gluck et al. 1994). It is quite possible that the truth lies between these two extremes; temporal and representational processes may not be explicitly dissociated, but some brain regions may specialize in one or the other. Thus, the entorhinal cortex could well mediate both representational compression and intermediate-term buffering, consistent with the spirit of both hypotheses.

A step linking memory to understanding?

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Eichenbaum, Otto & Cohen draw attention to the important distinction between the intermediate storage of information and the representational processing to which it may be subject; however, their concept of "relational processing" is still too imprecisely stated to allow unequivocal predictions and we will argue that the authors are relying upon experiments whose interpretation is at best ambiguous. We also question their concept of a "hippocampal system."

The valuable aspect of the target article is that it represents formal recognition that declarative memory might be fractionated into at least two semi-independent components. We think this separation represents a step towards linking memory to understanding. The authors' summary of the recent literature on delayed nonmatching to sample (DNMS) is excellent and we agree that it now seems likely that damage to certain cortical components of the medial temporal lobe disrupts the capacity to recognize recently presented individual items. A key set of experiments that remains to be completed involves investigating the effects of discrete, complete, neurotoxic lesions of other components of the medial temporal lobe, such as the hippocampus, upon intermediate recognition memory (as Mishkin's lab is already doing) and other types of memory. The only data of this type published to date have been obtained using the rat, and these suggest that hippocampal lesions are without effect on delay-dependent recognition memory.

Our first concern is the concept of a "hippocampal system" (sect. 1). This seems to be an arbitrarily chosen set of areas in roughly the same part of the brain having mono- or polysynaptic connections to the hippocampus proper and which, when damaged, sometimes cause deficits in memory of roughly the right kind to be consistent with Eichenbaum et al.'s theory. This seems to us logically incoherent, however. We make an appeal to all readers: to secure cumulative progress in neuroscience, let us all make appropriate use of anatomical and neuropsychological concepts. "Hippocampus" is an anatomical concept which refers to the CA cell areas only. It does not include even the dentate gyrus and certainly not the neocortical areas nearby. In contrast, Amaral and Witter's (1989) concept of the "hippocampal formation" is an anatomical concept based on specific criteria concerning circuitry (unidirectional connectivity). There may or may not be a multifunctional memory system, parts of which are located in the medial temporal lobe (we suspect there is), but anatomical adjectives are a misleading way of characterising it. The right descriptor, in fact the only descriptor at this stage of our understanding, has to be a functional one. We therefore suggest that a more appropriate title of this article might have been: "Two functional components of declarative memory."

Our second concern is with elements of the concept of a relational representation. It implies that an important aspect of the act of remembering, be it of facts or events, is "making comparisons" between stimuli and storing the "outcomes of these comparisons in terms of critical relations among items" (sect. 4.1). We agree. Absent from the variants of declarative memory theory until now has been any statement about how different types of memories are related, or anything about the frameworks through which we understand and remember the world about us. To store a fact, you have to understand a fact, and to understand a fact, you usually have to retrieve information from memory. The reference to "relational processing" is a step

in the right direction. However, the definitions of relational and individual representations offered in section 4.1 are too vague to allow precise predictions. For example, when does pairing an object with food result in an individual or a relational representation? We're still not sure. Within the realms of classical conditioning, there are, for example, situations in which control animals perform poorly to a reinforced stimulus when it is presented in a different context (Honey & Good 1993). This finding would seem to suggest that the representations are "inflexible in that they cannot be accessed or expressed in novel situations" (sect. 4.1). It seems odd, however, that under such conditions the performance of hippocampal lesioned animals was found to be unaffected. For this and other reasons, we doubt that this new binary taxonomic classification will stay the course, for it cannot capture the multidimensional aspects of memory representation any better than have previous taxonomies. It is now becoming increasingly apparent that even in procedurally simple tasks such as classical conditioning, a number of psychological processes are engaged (Holland 1993).

Our third concern is with the ambiguity of some of the data upon which the relational processing concept is built. A key pair of findings are the ingenious experiments of Eichenbaum et al. (1988; 1989) indicating that fornix lesions can (1) impair simultaneous odor discriminations but facilitate successive discriminations; and (2) cause rats to show chance performance when odor pairs previously used together in training (e.g., A+ B−, C+ D−, etc.) were mispaired (A+ with D−). We suspect, however, that both results have been misinterpreted. In the simultaneous discrimination task, the latency data of the control group showed a striking bimodal distribution (see Eichenbaum 1990, Fig. 19). This arose because the control rats showed position habits. They consistently approached (say) the left port and either kept their nose there when S+ was presented to the left (fast responses) or withdrew it when S− was presented and then responded to the right port containing the correct S+ odor (slow responses). For reasons that are still not clear, the fornix lesioned rats kept their noses about midway between each port, sampled both odors together, and then responded as quickly to the left or to the right. Thus, the control rats had effectively learned an easier problem than the fornix lesioned rats within the one procedure. That the control rats could subsequently deal with mispairing of odors and the fornix lesioned rats could not is hardly surprising as only the controls had turned the simultaneous task into a successive one through their odor sampling strategy and were thus capable of reacting appropriately to any S+ being paired with any S−.

Even if this simpler account seems unpersuasive, there is a puzzle about Eichenbaum et al.'s relational interpretation. It predicts that only control animals will engage in relational processing because only they can "compare and contrast individual items" and "capture the relevant relations between them." It follows that only control animals should learn that A+ has been presented alongside B−, that C+ has had a particular relation to D−, and so on. The fornix lesioned animals should not engage in this relational processing. Thus, the theory incorrectly predicts a performance deficit in control rats to the mispairing of odors whereas the fornix lesioned animals should be unaffected. Precisely the opposite result obtains – as our odor-sampling strategy analysis correctly predicts. Reference to phrases like "flexible use of representations" may seem to save the day, but doesn't carry conviction because it is an assertion after the fact rather than a deduction from fundamental principles.

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Psychoarithmetic or pick your own?

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Eichenbaum, Otto & Cohen "question the utility of straightforward tabulations because such an exercise inevitably leads to a sort of *psychoarithmetic* by which conclusions are made according to the simple majority of data." Instead, they pick and choose those experiments which, in their view, demonstrate how the putative "properties of hippocampal system-dependent learning" manifest themselves in animals with damage to this system. The difficulty with this approach is that, unless one has an independent criterion for the selection of such experiments, one theorist can make out a case for his preferred theory using one *experimentum crucis*, while another does the same using a second. To illustrate this dilemma, consider Eichenbaum et al.'s discussion of discrimination learning (sect. 4.2).

As indicated by the authors, the relevant psychoarithmetic appears in Tables 20, 21, and 22 of the review by Gray and McNaughton (1983) of the literature up to that date. The first two of these tables deals with the effects of hippocampal lesions on simultaneous discrimination, the third with successive discrimination.

With regard to simultaneous discrimination, Gray and McNaughton (1983, p. 160) state that "the most common finding has been no effect" of hippocampal lesions. However, "roughly one third of the reported findings found a difference between hippocampal and control groups, always in the direction of an impairment after the lesion. In most of these exceptional cases there are evident special factors at work." They go on to list the most important of these special factors as: presence of an initial preference opposed to the correct response; prior learning of a discrimination different from the one on which the animals are currently tested; and an excess of sources of interference (e.g., a large number of negative cues). The role played by these special factors is readily compatible with one of the oldest views of hippocampal function (but one that has been conveniently forgotten – *not* discredited – in these heady days of the cognitive revolution), namely, that the hippocampus is concerned with the inhibition of maladaptive responses (Douglas 1967). Gray and McNaughton therefore conclude that "nearly all of the impairments seen after hippocampal lesions can be accounted for without assuming any fundamental change in the performance of the simultaneous discrimination itself."

With regard to successive discrimination, Gray and McNaughton (1983, p. 164) state that, after hippocampal lesions, "there is a clear preponderance of reported impairments," which usually took the form of "increased responses in the presence of the negative stimulus." This observation, too, is compatible with the hypothesis that such lesions lead to a deficit in response inhibition.

Psychoarithmetic, then, rather clearly indicates that, in general, simultaneous discriminations tend less often to be disrupted by hippocampal lesions than successive discriminations. Eichenbaum et al. however, prefer their own experiments. These involved rats with fornix lesions tested with olfactory cures, and demonstrated severe and persistent impairments in a *simultaneous* discrimination coupled with no effect or even improvement (relative to controls) in a *successive* discrimination (Eichenbaum et al. 1988; 1989; Otto et al. 1991). Psychoarithmetic having been cast aside, Eichenbaum et al. see no reason to comment upon the flagrant contradiction between these results and the bulk of the previous literature. Others might be tempted to seek a reason for the contradiction. One possibility is the stimulus dimension used. There is indeed evidence that deficits in discrimination learning after lesions to the hippocampal system are affected by stimulus modality. Two studies have reported that rats with hippocampal lesions are

impaired if the discrimination involves visual stimuli, but not with thermal or tactile stimuli (Harley 1979; Plunkett & Faulds 1979). After septal lesions, which (psychoarithmetically speaking) produce a profile of change very similar to that seen after hippocampal lesions (Gray & McNaughton 1983; Vom Saal et al. 1975), using olfactory cues, observed, usually, *improved* successive discrimination. Thus, olfaction is a good candidate to account for the unusual pattern of results observed by Eichenbaum et al.

Whatever accounts for this unusual pattern of results, why should they command more attention than the rather large number of other experiments disregarded in the target article? If there is something different about the effects of hippocampal-system damage on olfactory and visual discriminations, respectively, there is no clear reason to regard one or the other as somehow going closer to the heart of hippocampal function. Eichenbaum et al.'s own reason is that they are able to make sense out of the findings with odour discriminations in the light of their own theory: the simultaneous discrimination task encouraged "stimulus comparisons and selection among alternative stimulus choices" (a process which, their theory holds, engages the hippocampal system), whereas in the successive discrimination "no stimulus choice was required" (sect. 4.2). Possibly, but why would not the same argument hold in modalities other than the olfactory (or, perhaps, in other laboratories, if stimulus modality does not, after all, play a critical role in determining the unusual nature of Eichenbaum et al.'s findings)?

Another worrying feature of this line of argument lies in the interpretation given in the target article to the difference observed between the susceptibility of simultaneous and successive discriminations, respectively, to fornix damage. It would have been equally possible to suppose that *successive* discriminations require "stimulus comparisons and selection among alternative stimulus choices," and indeed harder ones than simultaneous discriminations, since the required comparison involves retrieval from memory of the stimulus not currently present in perception. In this way, Eichenbaum et al. might have been able to reach the same endpoint with psychoarithmetic as by picking their own experiments – but only, of course, because of a worrying degree of flexibility in the theoretical arguments employed.

Given Eichenbaum et al.'s emphasis on the allocation of different functions to different regions (specifically, the hippocampal formation and the parahippocampal region), one would have expected more attention to the specific types and amounts of damage caused by different methods (e.g., electrolytic vs. excitoxic) of lesioning these regions. Surprisingly, however, Eichenbaum et al. fail to address these issues. In particular, it is unwise to assume that fornix transection (used in their own discrimination experiments, as noted above) has the same effects as ablation of the hippocampus. For example, Jarrard (1986; 1993) finds a different pattern of behavioral change in the radial maze after such ablation than do Olton et al. (1979; 1982) after fornix section. Existing techniques make it possible to achieve highly selective lesions to particular hippocampal subfields (e.g., Jarrard 1986; 1993), to eliminate particular transmitter pathways (e.g., serotonergic afferents, by 5-7 dihydroxytryptamine infusions into the fornix, Williams & Azmitia 1981) or to disable particular classes of receptor (e.g., by AP5 infusions into lateral ventricles to block N-methyl-D-aspartate [NMDA] receptors, Morris et al. 1986). Thus it is now possible to look for fine grained structure-function relationships than the dissociation between the hippocampal formation and the parahippocampal region favoured by Eichenbaum et al. Such relationships should provide more stringent tests of their theory, but they may also force departure from the grand tradition of unified theories of hippocampal function to which the target article belongs.

As befits a commentary, we have focussed upon criticisms of Eichenbaum et al. We conclude, however, on a positive note: we believe their theory to be a major step forward and on the right lines, both in the basic psychological processes it calls upon and in the way it allocates these processes to the hippocampal formation and parahippocampal region respectively. Like other theories in the grand tradition, it will not be easy to submit to experimental test, but it will surely – and deservedly – stimulate attempts to devise such tests.

Hippocampal modulation of recognition, conditioning, timing, and space: Why so many functions?

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Neural models of how animals and humans learn to adapt rapidly to changing environmental circumstances in real time have suggested how the hippocampal system may play multiple roles in recognition memory, attention, cognitive-emotional interactions, adaptive timing, and spatial orientation. One model concerns how humans and animals rapidly learn to categorize events and their contexts in real time. Interactions between inferotemporal (IT) cortex and the hippocampal formation are particularly emphasized. An attentional subsystem carries out the learning of bottom-up recognition categories and top-down expectations by interacting with an orienting subsystem that triggers reset and memory search for new or better categories when an input exemplar is too novel to match an active top-down prototype. The attentional subsystem models aspects of IT cortex and the orienting subsystem models part of the hippocampal formation. Together, these models make up an adaptive resonance theory (ART) model. A lesion of the ART model's orienting subsystem creates a formal memory disorder much like the medial temporal amnesia that is caused in animals and patient H.M. after hippocampal system lesions (Carpenter & Grossberg 1993; Grossberg 1975; 1982). ART clarifies how the hippocampal system achieves "flexible expression of memories in novel contexts" and why hippocampal neurons respond differently to match and nonmatch conditions (Otto & Eichenbaum 1992b; Riches et al. 1991; Sakurai 1990b). Indeed, mismatches within the attentional system trigger memory searches for better recognition categories by activating the orienting subsystem.

These modelling results do not support the claim that "representational properties of the hippocampal system comprise the fundamental characteristics of declarative memory." In fact, *no* memories are stored within an ART orienting subsystem. Rather, interactions between the orienting and attentional subsystem enable the latter rapidly and stably to learn to categorize new information in a way that is sensitive to environmental relationships.

Eichenbaum et al. dichotomize the temporal and representational properties of hippocampal memory processing as "orthogonal functional properties." A neural model suggests how these processes are linked. This model concerns how classical and instrumental conditioning are cognitively modulated and adaptively timed. Three types of internal representations interact within the model during conditioning: sensory representations (S), drive representations (D) and motor representations (M) (Grossberg 1971; 1975; 1987). The S representations are categorical representations of external events. The D representations are sites where reinforcing and homeostatic cues converge to generate emotional reactions and motivational decisions. The M representations control discrete adaptive responses. Three types of learning take place among these representation: S → D conditioned reinforcer learning; D → S incentive motivational

learning; and S → M motor learning. Learned S → D → S positive feedback quickly draws attention to motivationally salient cues and blocks activation of less salient cues via lateral inhibition among the S categories (Grossbert 1987; 1988). D → S feedback also energizes the release of discrete adaptive S → M responses. Grossberg (1971; 1975) suggested that drive representations (D), at or after the stage at which motivational decisions are made, intersect or are modulated by the hippocampal formation, consistent with data showing that conditioned emotional S → D conditioning influences hippocampal circuits, whereas S → M motor conditioning includes the cerebellum (Thompson et al. 1987). Moreover, hippocampal ablation attenuates blocking, the process whereby a more salient cue can normally inhibit processing of a simultaneous, but less salient, clue (Rickert et al. 1978; Solomon 1977). These properties clarify how "hippocampal system damage can result in either impaired or abnormally strong utilization of contextual cues" due to a failure of blocking combined with a failure of flexible reset and memory search.

How does the hippocampal formation modulate emotional conditioning? In the model, S → D → S feedback rapidly draws attention to motivationally salient cues, as inhibition from D to the orienting subsystem inhibits orienting responses to irrelevant situational cues. Another process *maintains* attention during variable task-related delays (Grossberg & Merrill 1992; Grossberg & Schmajuk 1989). For example, suppose that an animal inspects a food box right after a signal occurs that predicts food delivery in 6 seconds. Why does the mismatch between the expectation of food and the percept of no-food fail to trigger premature reset of attention, extinction, and exploratory behavior? The model suggests how a "spectral timing" circuit S → T operates in parallel with the fast S → D emotional conditioning circuit. Learned S → T timing prolongs inhibition of the orienting subsystem and maintains attention on goal-related cues within the 6-second delay. Thereafter, the adaptive timing circuit becomes quiet. Subsequent mismatches do trigger attentional reset, extinction, and exploration. Grossberg and Merrill (1992) assigned spectral timing to the dentate-CA3 circuit to explain many conditioning data; see Berger et al. (1986). Nowak and Berger (1992) have reported evidence at dentate cells consistent with the model's spatially organized spectral representation.

"Both DNMS performance at brief delays and single-pair object discrimination learning with brief intertrial intervals" are spared in hippocampal subjects. In the model, even if the T circuit is removed, the fast S → D → S attentional circuit remains intact. Long interstimulus delays, say of a day, also spare the performance of animals in some conditions (Mishkin et al. 1984). Eichenbaum et al. therefore claim that "the hippocampal system subserves a memory store of *intermediate* duration." The model does not posit any such "memory store." At short delays, the fast feedback S → D → S system helps to focus attention. The failure of blocking at intermediate delays due to removal of the S → T circuit causes little problem at long delays because potentially competing cues, being widely separated in time, decay before they can compete.

ACKNOWLEDGMENTS

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Hippocampal representations of DMS/DNMS in the rat

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The characterization of hippocampal-system-dependent memory proposed by Eichenbaum, Otto & Cohen and the model elaborated to explain this process distinguish two critical aspects of memory storage and retrieval: (1) temporal constraint and (2) relational representation of events. Temporal registration is relegated to brain regions adjacent to the hippocampus proper, that is, the parahippocampal region, whereas the hippocampus itself is stipulated to encode only relational aspects of particular stimuli. Such a model accounts for several well-known types of hippocampal deficits, including those recently reported describing a smaller deficit in delayed nonmatching-to-sample (DNMS) tasks from hippocampal versus parahippocampal or perirhinal cortical lesions (Zola-Morgan et al. 1989c).

In this model, hippocampal cell firing only represents a portion of a larger set of possible aspects of stimuli encoded into memory. The basic notion is that different qualities of the stimulus are "extracted" in different brain regions (cortex, parahippocampal region, hippocampus), as well as different temporal domains of DNMS, or of a delayed match to-sample (DMS) task, in order to specify the storage and retrieval required for a particular trial or across several trials. The final stage of stimulus processing is represented by the relational encoding of contextual information in the hippocampus, in which hippocampal cells fire only when the identified "conjunctive" relationship exists between the sensory stimuli and the context in which it occurs. After an extensive literature review and consideration of their own findings, Eichenbaum et al. assert that the hippocampus receives information from the neocortical and parahippocampal regions and makes the comparison of "relational representations," which triggers hippocampal cell discharge.

Based on the literature reviewed and our own findings from recordings of hippocampal neurons during *spatial* DMS and DNMS tasks, we find two aspects of this assertion difficult to agree with. First, we have documented that different types of firing patterns are exhibited by hippocampal neurons in the DMS/DNMS paradigm. The subtypes of firing conform to different temporal phases as well as different conceptual aspects (e.g., spatial location of the levers) of the task. Second, delay-type firing, which Eichenbaum et al. attribute to areas outside the hippocampus, has been documented to occur in the hippocampus during DMS/DNMS performance (Hampson et al. 1993a; 1993b). In the latter case we reported that at least one third of these neurons demonstrated consistent increases in firing during the delay period.

In our prior findings, it was demonstrated both quantitatively and via statistical partitioning, the conceptual aspects of the DMS task were represented in a manner distinctly different from the spatial features of the stimuli, and it was clear that both could be encoded by the same neurons. A simple example involves hippocampal cells, which showed a spatial bias to fire only when the left lever was pressed in the sample and match phases of the task, yet also showed a consistent increase in firing during the match phase on correct versus incorrect trials (Hampson et al. 1993b). It is difficult to understand how such a neuron, under Eichenbaum et al.'s classification, could fail to be responding to a "relational representation," yet the existence of a spatial firing bias to only one lever would also have to be categorized as item-specific sensory firing. Clearly, in the broad sense, this neuron fits their classification; however, the degree of control imparted by each of the individual factors was drastically different (85% spatial control versus 15% task control). Other hippocampal neurons were observed in which this degree of spatial and task control was different, illustrating that the

degree of convergence and resulting conjunctive firing of hippocampal neurons is quite variable.

In the primate and rodent literature cited by Eichenbaum et al., there is a definite tendency to focus on those cells encountered in particular brain areas that have peculiar firing properties. In almost all instances, however, cells with other firing characteristics, sometimes even opposite those of interest, were also reported. A more conservative application of Eichenbaum et al.'s model would provide for the existence of all cell types in each of the brain regions discussed, with perhaps only the proportions of the different cell types changing as one proceeds from neocortex to hippocampus. At the very least, it is misleading to state that descriptions of relational versus other types of firing, as defined in the target article, were confined to *only* hippocampal neurons, in either the primate rodent or (for that matter) even human literature (Heit et al. 1990).

Second, in our studies, 34% of hippocampal cells, regardless of type of conjunctive firing pattern, showed a linear increase in firing across the delay interval of the DMS task (Hampson et al. 1993b; Heyser et al. 1993). In quite recent studies (Hampson et al. 1992; 1993a), using many neuron-recording techniques, we have identified distinct differences in delay phase firing correlates of CA1 and CA3 neurons. Figure 1 shows three different temporal delay firing patterns recorded from four different hippocampal neurons within the same animal during DMS performance. The histograms are synchronized to the match response (MR), with the mean sample response (SR, onset of the delay) and sample presentation (SP) occurrences indicated on the bottom axis. The time region corresponding to delay interval firing (from SR to MR) is indicated by the arrows. The firing pattern shown by Neuron 1 is similar to the sustained firing cited by Eichenbaum et al. for neocortical units (Fig. 4a). Neuron 2 shows a peak in firing near the onset of the delay phase, followed by a gradual decrease in firing toward the end at the time of the match response. Neurons 3 and 4 show a "ramp-type" linear increase throughout the delay but the peak of firing is temporally

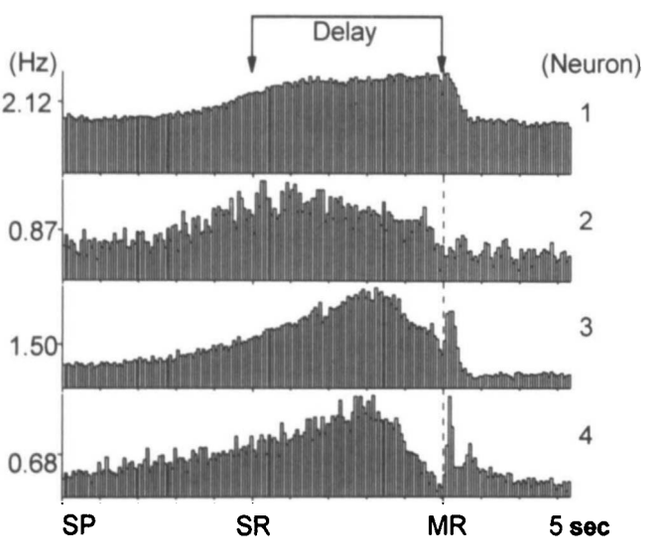

Figure 1 (Hampson and Deadwyler). Four neurons recorded from rat hippocampus during performance of a delayed match-to-sample task. Histograms show firing from the sample (SP to SR), delay (SR to MR) and match (MR to end) phases of the task. The neurons showed a combination of delay phase firing as well as event-related firing (i.e., post-MR peaks in neurons 3 and 4). Neurons were also recorded that showed no delay-related firing; however, the three distinct patterns evident here were typical of the combinations of delay and event firing correlates observed. SP: sample lever presentation; SR: sample barpress response; MR: match barpress response; mean firing rate (Hz) is shown for each neuron.

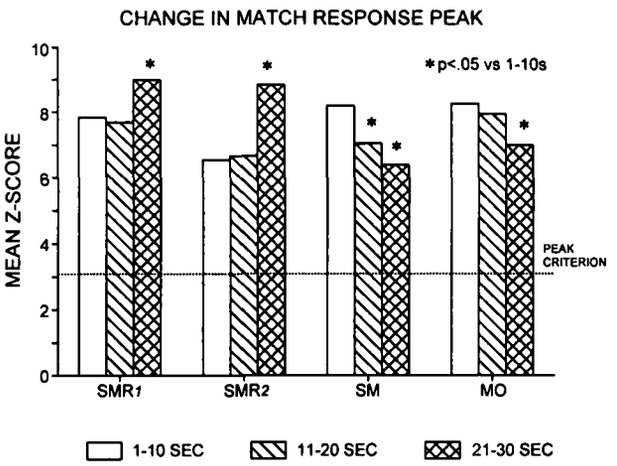

Figure 2 (Hampson and Deadwyler). Changes in match phase firing with increasing delay intervals. Bargraphs show post-MR changes in firing as standard scores (Z-score) of post-versus pre-MR firing rate [(post-MR-peak − pre-MR-peak) ÷ pre-MR-std.dev.]. Peaks with Z-scores > 3.09 (peak criterion) represented significant ($p < 0.001$) increases in firing from pre-MR. Trials were sorted according to length of the delay interval, and peak Z-scores were averaged for trials consisting of 1-10, 11-20, and 21-30 sec delays. Asterisks denote significant ($p < 0.05$) differences in peak Z-scores for 11-20 or 21-30 sec delay trials as compared to 1-10 sec trials. Subtypes refer to the event-related firing peaks exhibited by those neurons: SMR_1: sample-match-response type 1; SMR_2 sample-match-response type 2; SM: sample-match; MO: match-only.

different as previously described (Hampson et al. 1993b). Neuron 4 (and to a lesser extent, Neuron 3) also show a distinct firing peak after the match response that followed a decrease in delay firing. It is unlikely that these neurons have encoded "unidentified behavioral events" occurring during the delay as described in section 5.3 of the target article, since they exhibited *differential* firing when the delay period behavior was "clamped" by forcing the animal to nosepoke (see Hampson et al. 1993b). Thus, neural activity correlates of DMS/DNMS that Eichenbaum et al. attribute to extrahippocampal areas can also be found within significant numbers of hippocampal neurons.

If hippocampal neural activity reflects only relational representations that depend on the prior temporary storage of events in parahippocampal areas, then the cellular representations of these events should deteriorate with increasing length of delay in the same manner as the behavioral performance. Of the four subtypes of hippocampal neurons previously recorded in this laboratory during DMS performance (Hampson et al. 1993b), two subtypes, sample-match (S-M) and match-only (M-O) showed a significant delay-dependent decrease in match-phase firing (mean *z*-scores, Fig. 2). However, the two most numerous subtypes, sample-match-reinforcement types 1 and 2 (SMR_1 and SMR_2), which encoded more complex features of the task, actually showed significantly *increased* firing following longer delays. The increase in magnitude of the match-phase firing following long delays indicates that this representation persists *despite* apparent decay of the behaviorally accessible information across delays! Given the diverse types of delay interval firing demonstrated in Figure 1, the increase in firing with longer delays could be generated by combining inputs from other hippocampal cells with variable delay firing attributes.

The neurophysiological results cited here do not dispute the fact that neurons in other brain regions can encode either relations between task-relevant events or delay-dependent sensory representations. They do, however, indicate that hippocampal neurons express combinations of responses to behavioral

events, and that the types of processing correlates that Eichenbaum et al. attribute to separate areas of the brain can also be demonstrated by different cells within the hippocampus. Based on the literature cited, it would not be surprising to find "representations" of a similar nature in some neurons in all of the implicated brain regions in their model, the difference from hippocampus being only in the *proportion* of *relational* representations versus other types. Therefore a strict distinction between any of these brain regions with respect to an exclusive type of processing critical to memory should be viewed as tentative at best.

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The localization of general memory functions

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At one time, we proposed that medial temporal lobe amnesia resulted from damage to the temporal stem, the white matter connecting temporal cortex, instead of the hippocampus (Horel 1978). Although we have changed our views on this somewhat (Horel 1994), Eichenbaum et al. confirm the emphasis this places on the temporal cortex, attributing some of their memory functions directly to cortical structures that our subsequent research delineated. Our experiments suggest that a small part of temporal cortex selectively processes the functions required for delayed matching-to-sample (DMS) tasks. We used small reversible lesions and found deficits on this task only in the cortex and white matter of the temporal pole (Horel & Pitko 1982; Horel et al. 1984). On further exploration, we found that the area critical for the performance of this nominal measure of amnesia, included a strip extending along the inferior temporal and lateral parahippocampal gyri that was continuous with the temporal pole (George et al. 1989; Horel et al. 1987). We also found that the visual input to this cortex did not come by way of the classical pathways into inferotemporal cortex but by a separate pathway parallel to it (Martin-Elkins & Horel 1992); it has no direct input from most of classical inferotemporal cortex, which makes it awkward to assume the widespread input from cortical areas necessary for this model of generalized memory functions in the hippocampal system. Our behavioral results were consistent with this anatomy: very small lesions, including ablative lesions, in this ventral temporal cortex, but not elsewhere in the temporal lobe, produced powerful deficits on the task. Others have replicated our findings on the sensitivity of DMS performance to lesions in this cortex, but they have associated it with rhinal cortex in order to include it in the limbic system (as reviewed in the target article). We also found deficits on DMS with very small temporal stem lesions that cut pathways exiting dorsally from this anterior ventral temporal cortex (Cirillo et al. 1989). We found that temporal pole suppression produces a remarkable sensitivity to the effects of interfering stimuli, which does suggest a role in visual memory (Horel et al. 1984).

The hippocampus and amygdala have little or nothing to do with DMS. The effects of large medial temporal lobe lesions on this task came from damage to the same temporal cortex that we found on the ventral surface and probably also from damage to white matter in the temporal stem that feeds it (e.g., Murray 1992). Excitotoxic destruction of the hippocampus and amygdala, which spares the white matter of the temporal stem, does not affect performance on this task (O'Boyle et al. 1993). However well DMS diagnoses amnesia, it does not diagnose hippocampal damage. Eichenbaum et al. gerrymander the hippocampus to include the temporal cortex where lesions do produce deficits on DMS, creating a "hippocampal system" to accommodate this embarrassing result. They then assign to the area we identified with DMS on the ventral temporal lobe the task of holding the information that the hippocampus compares and relates.

Nonetheless, I take these findings to be consistent with our emphasis on the involvement of damage to temporal cortex or its white matter in temporal lobe amnesia. The issues I raise here concern not where an organ of memory is, but whether such a place exists (Horel 1994). Patient H.M.'s syndrome is the result of damage to this hippocampus, amygdala, overlying cortex, and temporal stem (Horel 1978). Since damage occurred to all of them, his symptoms must reflect their loss, not the loss of one component.

There is strong evidence for navigational functions in the hippocampus, but the desire to place a general organ of memory there motivated the attempt to broaden the implications of these findings. Eichenbaum et al. here propose that the hippocampus serves associations between stimuli, but almost before the ink dries on this idea, evidence emerges for associations between stimuli that are unaffected by hippocampal lesions (e.g., Cho & Kesner 1993; Davidson et al. 1993). All of the brain's functions require the proposed memory processes, and in the model presented they must all access the hippocampus, trucking information back and forth across broad expanses of cortex, taking many dubious anatomical steps to do so. Although it may be easier to conceptualize in the rat, imagine, doing all this with functions in perisylvian language areas, getting all of our word associations and their contexts into the hippocampus to bind them together, and, thus bound, returned to language areas. This trip must occur over vast areas of cortex, through many indirect steps. Aphasia obscures a memory impairment, but careful testing reveals that it is there (e.g., Risse et al. 1984), so why insist on this unlikely and unnecessary trip to the hippocampus and back?

What drives this compulsion to force general memory functions that are shared by widespread brain areas into the hippocampus, hippocampal system, or any other isolated structure? The functional subdividing of the cortex has been one of the great advances of our science, but does it parcel into memory areas and nonmemory areas, or areas that make associations between stimuli and context and areas that do not? Are there structures such as the hippocampus or rhinal cortex that serve memory *per se*, even a specialized memory, such as declarative memory? To have memory areas, there must be nonmemory areas. The failure to see amnesia with most brain lesions motivated the construction of special memory areas in the few places where it did occur (Horel 1994). The exclusion of the rest of the brain from performing memory functions follows from a *non sequitur:* if the lesions do not produce the syndrome of amnesia, but rather disorders of perception or aphasia and the like, the lesioned structure does not function in memory. These effects do not proscribe memory functions, however, but obscure them. Oddly, no one applies this faulty logic to the hippocampus or its system. No matter how compelling the evidence for its specialization, probably for some kind of navigational function, efforts continue to be launched, as in the target article, to rationalize a localized but general memory function consistent with hippocampal mythology. The list of memory functions not impaired by hippocampal lesions is now much too long to support this fiction.

Going from task descriptions to memory structures

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At the outset we would like to express our support for two interrelated positions taken by Eichenbaum et al. (sect. 4.1). We agree that humans and other animals have flexible memory systems and that these flexible systems may well depend partially or wholly on normal hippocampal functioning. We also agree that it is extremely unlikely that a particular task characteristic will be consistently associated with a deficit due to damage to the hippocampus. Similar positions have been put forward by Humphreys et al. (1989).

The concept of a relational representation has not been well defined by the authors, however, and the mapping between tasks and memory structures or processes requires further analysis. To start this process of relating task to structure consider the negative patterning task (sect. 4.5) used by Sutherland and Rudy (1989). A theoretically neutral way to describe this task is that it is *not* linearly separable. That is, if we assign numerical values of 1 and 0 to the presence and absence of the two inputs (A and B) and 1 and 0 to the two outputs (respond and do not respond), there is no linear function of the input values which allows us to map (1,0) and (0,1) onto one of the outputs and (0,0) and (1,1) onto the other output. Such a task can be learnt if the memory system can store information linking the three components. Humphreys et al. (1994) referred to this as a 3-way binding. These 3-way bindings may be compositional, or functionally compositional, in that they allow the recovery of the individual components (van Gelder 1990). They may also be noncompositional. Alternatively, nonlinearly separable tasks can be learnt in two stages by a system that stores pairwise bindings to intermediate representations. An illustration of the possibility of learning a nonlinearly separable task in two stages will be presented later.

In contrast to the 3-way bindings or 2-stage processes required for nonlinearly separable tasks, other tasks only require pairwise bindings. For example, Humphreys et al. (1989, 1994) have described the requirements for an animal to learn to approach or avoid an object that has previously been encountered in any situation (generalized recognition). This calls for the formation of a representation of the object, the ability to determine whether or not a representation exists in memory, and the attachment of an approach or avoidance response to the internal state, which results from determining that a memory representation does or does not exist. Thus, this requires more than just the ability to form a representation of an object as discussed by Eichenbaum et al. (sects. 3.1 and 4.1). Humphreys et al. (1989) had also noted that generalized recognition worked best with novel stimuli (sect. 3.1).

A 3-way binding that allows the recovery of the individual components can be described as relational and can be contrasted with the 2-way binding required for generalized recognition and other simple associative tasks. In the radial arm maze task (sect. 4.4), however, the animal must avoid an arm that has already been entered during the current episode. This task, like list-specific item recognition (Chappell & Humphreys 1994; Humphreys et al. 1989; 1994), only requires a 2-way binding (e.g., between a representation of the episode and the maze arm). By itself, the concept of relational memory does not explain why these tasks and the nonlinearly separable tasks are affected in a similar fashion by hippocampal lesions.

The simultaneous odor discrimination task (sect. 4.2) is also a puzzle because it does not appear to call for anything more complex than what is required for a comparable successive discrimination task. Yet the results clearly show that the simultaneous task is not learned in the same manner as the successive task (Eichenbaum et al. 1989). It is not necessary to conclude that there is a binding involving both stimuli in the simultaneous task. Instead, the rats could acquire an expectation about which odor will be rewarded and then they could check each odor source to see whether it matches their expectation. The approach response would then be attached to the outcome of the matching operation, not to a specific stimulus, as presumably happens in the successive discrimination task.

A very similar sequence of operations could also be used to solve the nonlinearly separable task used by Whishaw and Tomie (1991). Here there were two strings (T_1, T_2) and two odors (O_1, O_2). Rats had to choose T_1O_1 and T_2O_2 but avoid T_1O_2 and T_2O_1. To complete this task using only pairwise bindings, assume that one of the strings that is present on a particular trial is used to generate an expectation for a particular odor. This expectation would then be matched against the odor that is actually on the string and the approach or avoidance response would be attached to the outcome of the matching operation. Note that in the Whishaw and Tomie (1991) task the animal must sample a stimulus on each trial in order to generate an expectation, whereas in the Eichenbaum et al. (1989) task the expectation can be generated in advance of the trial.

This brief discussion of some of the problems involved in going from a description of tasks to the underlying memory components should help to make three related points. The first is that it is necessary to be explicit about the entire sequence of functions required to produce an output. Second, the explication of these functions may suggest additional ways to perform new tasks and alternative hypotheses about the functions computed by the hippocampus. Finally, it should be clear that a formal analysis of memories (bindings) and tasks is part of the problem in creating an animal model of human amnesia. Although we think that Eichenbaum et al.'s analysis is insufficient, this does not detract from their other contributions.

A call for greater concern regarding the underlying anatomy

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An important contribution of Eichenbaum et al.'s target article is to direct attention to the increasing emphasis now being placed on the involvement in memory of those allocortical areas adjacent to the hippocampus. In a recent talk at the European Brain and Behavior Society Meetings entitled "Monkey hippocampus and recognition memory: What went wrong?" Mort Mishkin pointed out that he and his colleagues were misled in thinking that the adjacent cortical areas necessarily damaged while removing hippocampus and amygdala by aspiration played only a minor role. The failure to fully appreciate the importance of extra damage to adjacent structures and pathways has also been a problem in attempting to interpret the results of lesion experiments involving other species, especially studies involving the rat (see Jarrard 1986; 1993).

Basing their model primarily on the results of neuropsychological investigations, the authors conclude that the important functional subdivisions of the "hippocampal system" are the hippocampal formation (which they describe as fornix, dentate gyrus, hippocampus proper, and subiculum) and the parahippocampal region (including entorhinal, perirhinal and parahippocampal cortices). What are the implications of grouping the structures in this way? Currently, there is considerable confusion in the literature regarding what different investigators mean by terms like hippocampus, subiculum, hippocampal lesion, hippocampal formation, and so on. It is unfortunate that there is not more agreement regarding the precise meaning and

use of these and related anatomical terms. Since the proposed grouping of structures differs from what most investigators have used in the past (especially "hippocampal formation"), one likely effect will be to add to the existing confusion. Even though, as pointed out by Patterson (1991), "an academic would rather use his colleague's toothbrush than use his terminology" (p. 40), I will use the authors' terms for the purpose of this commentary.

What about grouping the fornix, dentate gyrus, hippocampus proper, and subiculum together as a unit that mediates a specific process, for example, relational representation? Such a grouping of structures serves to minimize the exquisite anatomical differences within and between these various structures, and the functional differences that seem to exist (see Jarrard 1993). It is particularly unfortunate, in the opinion of this commentator that Eichenbaum et al. choose to equate the effects of a fornix lesion with a lesion of the hippocampal formation (sect. 1.2). Interrupting the axons in the fimbria-fornix is not the same as directly damaging the hippocampus (dentate gyrus, hippocampus proper) or subiculum – either in terms of changes in morphology or neurochemistry, or in terms of function. Moreover, although the effects on spatial tasks (radial and water mazes) of removing the cells that comprise the subiculum may seem similar to those of removing the hippocampus, there are important differences in the acquisition of nonspatial tasks (Jarrard 1993; also unpublished results). Grouping the structures and fiber bundles into a single unit with a single function would seem to increase the possibility that investigators will be misled in a manner analogous to what occurred in research involving medial temporal structures in lower primates.

A test of the adequacy of any model is the extent to which it accounts for relevant studies and makes experimental predictions testable. Does the current model meet these criteria as claimed by Eichenbaum et al.? Specifically, how well do the research findings agree with the notion that the hippocampal formation is crucial for relational representations, whereas the parahippocampal region mediates intermediate-term memory?

Relational representations are described as representations that are based on comparing and contrasting individual items. The theory predicts that animals with hippocampal formation damage will perform poorly when the demand for comparing and relating items is high. Is it possible to test this prediction? One task that should require "comparing and relating" items is the odor-guided "paired-associate" task designed by Bunsey and Eichenbaum (1993a; 1993b). In the task, two odors are presented, separated by a brief blank interval; the rats are required to compare the stimuli and respond when any one of four pairs are presented, but to withhold responding when the individual stimuli are "mispaired" or when any of the eight odors are presented together with other odors. Since learning this task requires comparing and relating items (e.g., "relational representations"), it is interesting that rats with the hippocampus removed not only failed to be impaired but learned the task more quickly than controls (see Bunsey & Eichenbaum 1993b). In an earlier study, rats with parahippocampal lesions were found to be impaired in the acquisition of the same task (Bunsey & Eichenbaum 1993a). The results of these studies were interpreted as indicating that "the hippocampus normally supports a representation of the relationships between paired odors and that, in the absence of hippocampal function, the parahippocampal region supports efficient learning by representing odor pairs as configural cues" (Bunsey & Eichenbaum 1993b). These results, and the interpretation that is offered, would seem to point out the difficulties involved in designing experiments to provide a priori tests of most theories in the area.

And how convincing is the evidence that the parahippocampal region but not the hippocampus mediates intermediate-term memory? Using the rule that "even single examples and counterexamples . . . are important and must be explained" (sect. 4.1), one can't help but wonder about the implications of a study we did that involved the forgetting of spatial versus intramaze cue information following selective removal of the hippocampus (Jarrard 1993). The task required learning a matching-to-place (or sample) rule in the radial maze where within a day the same arm (or cue) was correct on all five trials but different arms (or cues) were correct across days. After the rule was learned, delays (0, 5, 20, 60 min) were introduced between the last two trials of the day. Although there was little forgetting of spatial information in controls, rats without a hippocampus made an increasing number of errors as delays were increased. Even though the intramaze cue task proved to be more difficult for both groups, there was no evidence for differential forgetting in the hippocampal and control rats. For present purposes, the important point is that rats without a hippocampus *did* experience a delay-dependent impairment in retention, thus supporting a view that the hippocampus *is* involved in the temporary storage of (spatial) information. In a related experiment that involved entorhinal-perirhinal lesions and a delayed nonmatching-to-sample (DNMS) task, lesioned and control rats did not differ overall, but there was a tendency (nonsignificant) for the lesioned rats to be impaired at longer delays. These two experiments do not support predictions of the model.

A defining characteristic of the hippocampal function according to Eichenbaum et al. is the flexible expression of memories. Although the evidence for a lack of flexibility following hippocampal damage is convincing, one should also remember that this is not unique to damage involving the hippocampal system. In fact, there is considerable evidence for decreased flexibility following damage to a number of cortical areas (see Lashley's papers in Beach et al. 1960; Gisquet-Verrier & Delatour 1993).

A commentator is requested to provide "criticism, interpretation, elaboration, and so on" of the target article. Although the above comments may appear to be mostly critical, it is important to point out that the authors have done an admirable job of synthesizing a complicated, confusing, and contradictory literature. The emphasis has centered primarily around neuropsychological findings, and the many contradictions in the literature are attributed primarily to differences in behavioral testing procedures and resulting differences in processing demands. In my view, it is equally (if not *more*) important to emphasize the underlying anatomy and to consider differences in the nature and extent of the brain damage found in various lesion experiments (see Jarrard 1986; 1993). There is little question but that the "two functional components" view of hippocampal function proposed by Eichenbaum et al. will serve to sharpen our thinking about relevant issues – and this, in and of itself, represents a significant contribution!

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How long do relational representations in the hippocampus last during classical eyelid conditioning?

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In this target article, Eichenbaum, Otto & Cohen present an impressive breadth of empirical findings – findings that have often seemed hopelessly at odds with one another – as unified support for a two-stage conception of the "declarative" (Squire 1992) hippocampal memory system. The theory is plausible, although it awaits direct attempts at falsification. The present commentary will discuss data (generated mainly in this lab) that,

while consistent with the theory put forth in the target article, suggest two areas in which it could benefit from development and enrichment.

Central to the theory, Eichenbaum et al. assert that the hippocampal formation proper – consisting of the fornix, the dentate gyrus, Ammon's horn, and the subiculum – is critical for the development of "relational representations," whereby items in memory are compared and contrasted. According to this scheme, the hippocampus is not involved in the processing of individual stimuli. Multiple- and single-unit hippocampal recordings made during classical eyelid conditioning in the rabbit are in accord with this assertion: hippocampal activity comes to model the eyelid CR during basic delay conditioning, reflecting neither the presentation of the CS nor the US; no processing of independent stimuli appears to occur in the hippocampal formation (Berger & Thompson 1978). In contrast, activity in the cerebellar deep nuclei, generally understood to be critical for the learning of this response (Steinmetz et al. 1992), reflects presentation of the CS and the US and eventually execution of the CR (e.g., Berthier & Moore 1990). These data suggest that, unlike the hippocampus, the cerebellum processes individual stimuli and, moreover, promotes associations between the stimuli. Eichenbaum et al. suggest that the hippocampal model is available to the cerebellar circuit in the event of a task requiring a relational representation. In trace conditioning, for example, hippocampal processing is integral (Moyer et al. 1990).

This example of a hippocampal involvement in a memory system has little to do with the cortex, however. Although the physiology of connections between the hippocampus and the cerebellum is still something of a mystery, it is clear that the processing of the CS and US in this task is accomplished subcortically. Small lesions of the interpositus nucleus before training prevent CR-related activity in the hippocampus (Sears & Steinmetz 1990); post-training lesions abolish already established hippocampal modeling (Clark et al. 1984). It should be noted that trace conditioning is also prevented by cerebellar lesions (Stotler et al. 1990) despite the fact that the hippocampus continues to receive stimulus-related information following such lesions via at least one source, the medial septum (Miller & Steinmetz 1992). It seems that the cerebellum is critical for the development of the eyeblink response regardless of whether a relational representation is called for. In the eyelid conditioning paradigm, the cerebellum plays a role something like the one that the Eichenbaum et al. model attributes solely to cortical structures. In fact, many of the avenues by which the hippocampus may be recruited to assist in memory formation may be noncortical. In concentrating solely on cortico-limbic connections, Eichenbaum et al. fail to give an accounting of the full system available to the animal.

Granted that the hippocampus is implicated in trace conditioning (Moyer et al. 1990), the time-course of its involvement is another phenomenon yet to be explored. Sears and Steinmetz (1990) have recently examined hippocampal activity across sessions in delay conditioning of the rabbit eyelid. In the absence of an effective cerebellar lesion, hippocampal activity across nine days of testing was found to resemble an inverted-U-shaped function. The hippocampus became more active over the first four or five sessions, after which it returned to baseline levels of responsiveness. Significant development of the behavioral response occurred only as hippocampal activity declined to its lowest levels. Sears and Steinmetz briefly switched conditioning to the other eye, establishing hippocampal activity quickly; when training was switched back, activation again resembled an inverted-U-shaped function, despite the previous establishment of solid behavioral response. Preliminary work from this lab suggests that the same pattern holds in the context of trace conditioning (Steinmetz, unpublished data).

These data present interesting questions for Eichenbaum et al. It seems possible that trace conditioning requires the hippocampus only at certain stages of training. A hippocampal lesion inflicted early in training may prevent development of the CR, whereas a lesion created later in training may be found to have no effect. Furthermore, hippocampal activation may be dissociable from changes in performance. This is an issue of context that is fundamentally different from the one extensively discussed in the target article: neural recruitment may vary not only with the specific task parameters, but also through time, on a task with constant parameters. Reference to the time-limited behavior of the hippocampal memory system in general also has to do with manipulation of task parameters such as the interstimulus interval (ISI) (Squire 1987; 1992) and is thus also tangential. Is the conclusion, therefore, that trace conditioning is a relational task early on, but not later? From this perspective, the term "relational" becomes ambiguous and difficult to apply, and the term "involvement" is seen to be somewhat too black and white. We would find it interesting to know Eichenbaum et al.'s hypothesis concerning how hippocampal involvement in memory tasks changes as a function of time and experience and what the implications of these changes are for their theory of memory.

Hippocampus and memory for time

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In this commentary I will deal with the issue of the role of the hippocampus in mediating time. It is assumed by Eichenbaum et al. that the persistence and strength of memory processing of relationships are represented in an intermediate memory storage system, a system that bridges the gap between short-term memory (STM) and long-term memory (LTM). The critical question concerns the limits placed on the time course of STM and intermediate-term memory (ITM).

In the human literature it has been suggested that STM for individual items can last up to at least 18 sec (Peterson & Peterson 1959). If one uses this observation as an estimation of the upper limit of STM and the lower limit of ITM, then according to the proposed model there should not be any deficits in relationship-mediated tasks (spatial) in which delays less than 10 sec are used. However, there are a number of studies indicating that rats or monkeys with hippocampal system lesions are impaired in spatial tasks at very short delays (less than 10 sec; Jackson-Smith et al. 1993; Kesner 1990; Kesner et al. 1988; Parkinson et al. 1988), suggesting that the hippocampal system mediates short- as well as intermediate-term memory for spatial relationships; that is, the hippocampal system serves as a neural system that encodes temporary relationships in both STM and ITM.

Jackson-Smith et al. (1993) tested rats in a continuous recognition memory task for spatial location information. In this task daily sessions involved sequential presentation of individual arms on a 12-arm radial maze. Each arm contained a reinforcement the first time it was presented. A subset of the arms was repeated, but did not contain reinforcement. Repeated arms were presented with lags ranging from 0 to 6 (0 to 6 different arm presentations occurred between the first and the repeated presentation). Following large electrolytic lesions of the hippocampus, there was a total deficit in performance, even at the zero lag (relatively short time interval). This deficit could not be assigned to a problem of response inhibition, because in a procedurally similar continuous recognition memory for objects task, there were no deficits in performance.

In a different study, Parkinson et al. (1988) showed that monkeys with hippocampal lesions were impaired in memory for an object-place task even at delays of 6 sec. The monkeys

were not able to learn this task even after 1800 trials. However, they had no difficulty performing an object memory task with 10 sec delays, so that the difficulty in the object-place task could not be assigned to a general inability to perform a memory task.

In a final study, Kesner et al. (1988) showed that in a spatial location recognition memory task for a list of 5 spatial locations, small dorsal hippocampal lesions disrupted memory for all but the last item (recency effect), suggesting that STM was intact. However, large dorsal hippocampal lesions produced a deficit for all items within the list, suggesting that there is no STM representation of spatial information with a sufficiently large dorsal hippocampal lesion. The possibility exists that the larger the lesion, the greater the probability of disruption of STM. It should be noted that large entorhinal cortex lesions also produced a complete deficit for all spatial locations in the list (Johnson & Kesner 1993).

The proposed model cannot very easily incorporate these data in an ITM system and thus the basic premise that the hippocampus and entorhinal cortex can only encode relationship information in ITM is problematic and needs to be altered to include STM.

Even though there are few, if any, differences between the parahippocampal region and hippocampus in temporal processing of spatial information, major differences do emerge for memory for single items (objects, odors), in that hippocampal lesions do not appear to produce memory deficits, whereas parahippocampal lesions produce profound memory deficits (see sect. 1.2). These data suggest that the hippocampus and parahippocampal region might serve parallel temporary memory storage functions (STM and ITM) for spatial (relational) and sensory-perceptual (individual) attribute information, respectively.

In the proposed model, the hippocampal system mediates time as a process involving strength and persistence, but not as a critical functional component of mnemonic relationship representations. Thus, time as a process is orthogonal to time as a memory representation. I have suggested (Kesner 1990) that the hippocampus mediates time as an integral component of relationships as reflected by memory for duration of events and memory for temporal order of events. Relationship qualities can be ascribed to (1) the duration of an event, in that events have a beginning and an end that need to be related across time for duration to be remembered, and (2) to the temporal order of events, in that comparisons need to be made among events in order to remember which occurred earlier or later in time. Furthermore, duration or temporal order can be remembered across delays in STM paradigms, that is, temporal information can be processed dynamically in terms of strength and persistence of storage.

Support for these ideas comes from experiments demonstrating that hippocampally lesioned rats are impaired remembering the temporal order of spatial locations (Chiba et al. 1993) and the durations in delayed conditional discrimination of duration (Jackson-Smith et al. unpublished observations).

In summary, I have suggested that from (a) a dynamic point of view, the hippocampal system (hippocampus and entorhinal cortex) processes information for a relatively short time period, but that this time period cannot be assigned exclusively to short- or intermediate-term memory, especially for spatial relationships; and from (b) a structural-representational point of view, it processes temporal information, such as duration and temporal order, in order to enhance the role of the hippocampus in mediating temporal-spatial relationships. In contrast, Eichenbaum et al.'s proposed model does not provide a dimension for representing relationships in the hippocampus.

What exactly do amnesics fail to store normally?

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Eichenbaum, Otto & Cohen's hypothesis about hippocampal and parahippocampal functions suggests that organic amnesia comprises at least two functional disorders that may often occur together. First, amnesia caused by parahippocampal lesions involves a disturbance of intermediate-duration storage for individual items and a resultant further deficit in relational memory processes. Second, amnesia caused by lesions of the hippocampus or fornix involves a selective disruption of relational memory.

The hypothesis is valuable in integrating findings from several sources, but needs to be more fully articulated before its appropriateness as an account of the phenomena of human amnesia can be properly assessed. In this commentary, I shall indicate four areas where the implications of the hypothesis need greater clarification, describing some recent findings relevant to one of these areas.

First, the hypothesis focuses on medial temporal structures, but amnesics with midline diencephalic lesions show memory deficits very similar to those with medial temporal lobe lesions. Do the authors believe that fornix, anterior thalamus, mammillothalamic tract and, possibly, mammillary body lesions have effects identical to those of hippocampal lesions? If midline thalamic lesions not involving the hippocampal circuit contribute to amnesia, will these lesions cause a unique pattern of memory deficit, or one similar to that caused by parahippocampal lesions?

Second, does the hypothesis imply that parahippocampal or hippocampal lesions cause a retrograde amnesia, and, if so, what will its temporal characteristics be? As damage to the hippocampal system should disrupt the long-term storage of relational representations, one might expect that such lesions will cause a retrograde amnesia with a flat gradient whereas parahippocampal lesions will cause an initially steeply graded retrograde amnesia for "items" as well as relations and a flat gradient for relations stored some time before brain trauma. A gradient following hippocampal lesions would only be predicted if one argued, like Squire (1992), that relevant memories eventually become independent of the hippocampus.

Third, should amnesics show impaired priming for certain kinds of novel information, with the exact kinds affected depending on lesion location? Priming (or implicit memory specific to trained materials) for information that is novel prior to the training experience must involve the creation of new memories. If priming and explicit memory tests tap memory for either identical or very similar information, then it is probable that they draw on strongly overlapping memory representations. Rejection of this position would depend on very convincing evidence, that does not exist at present. If parahippocampal lesions disrupt intermediate memory storage for integrated representations of novel items, these lesions should impair priming for any kind of novel item (such as nonwords or new faces). There is some evidence against this position (for example, see Squire 1992), so either the hypothesis is wrong, the data are misleading, or a different account of priming has to be correct. If hippocampal circuit lesions prevent the storage of relational representations, one might argue that priming for certain kinds of novel associations should be disrupted. This should occur when subjects have to retrieve an item that has been associated during training with an item presented at test, as in enhanced stem completion priming. There is evidence that amnesics do not show such priming to a normal degree (Mayes & Gooding 1989), although there is controversy about whether performance on indirect memory tasks of this kind may be abnormal in

amnesics because normal performance is often partially mediated by their superior explicit memory. Many workers, however, have argued that these kinds of associative priming lack the flexibility of explicit memory for the same associations, and flexibility is a defining feature of relational representations. To clarify the predictions of the hypothesis about amnesic priming, Eichenbaum et al. need to specify more fully (a) what is stored in the parahippocampal system, (b) the meaning of a relational representation, and the concept of flexibility (which seems to have more to do with the retrieval than the storage system), and (c) the properties of the "inflexible" hippocampal-independent memories.

Fourth, should some or all amnesics show accelerated loss of explicit memory according to the hypothesis? It seems to require parahippocampal and hippocampal lesions to disrupt the storage of novel items and relational associations and of novel relational associations, respectively. So amnesics with appropriate lesions should show accelerated loss of explicit memory during the time when the storage processes that have been disrupted in amnesics are occurring in normal subjects. For certain kinds of explicit memory, therefore, the size of the amnesic deficit should increase in the minutes following learning. In unpublished work, Isaac and I have examined the rate of loss of free recall, cued recall, and recognition at delays between 15/20 seconds and ten minutes, matching initial memory levels in patient and control by giving patients more learning trials. Amnesics with medial temporal lesions (including a case with relatively selective hippocampal lesions) and midline diencephalic lesions (including a case with relatively selective mammillary body lesions who was tested by Dr. Kapur) showed accelerated loss of free recall, but *not* of cued recall and recognition, for short stories at delays over the tested interval. The effect was found *regardless of the lesion location that caused amnesia* and further work showed that: (a) it was not explicable in terms of residual, normal short-term memory contributing to amnesic-free recall at the shortest but not the longest delay; (b) surreptitious rehearsal by the control subjects during the longer delays; (c) an artifact caused by the procedure used to match amnesic and control explicit memory at the shortest delay; (d) excessive sensitivity to interference by the amnesics at the shortest delay, which, if it had been found, would explain the effect in terms of a retrieval deficit. In a second study, we found a similar effect with word lists comprising categorized words arranged either randomly or in an organized fashion. When subjects were tested with lists of unrelated words, however, we, like Haist et al. (1992), found that free recall as well as cued recall and recognition was lost at a normal rate in amnesics. With such lists, normal subjects find it hard to form interword associations in one trial.

We interpret these results as indicating that amnesics with both medial temporal and diencephalic lesions are impaired at storing complex associations between two or more items and their background context. Free recall of stories and categorized lists depends heavily on retrieving such associations, but cued recall and recognition (in our tasks) probably depended either on retrieving simple item-context associations or on item familiarity, both of which are either unaffected or much less affected in amnesics. If a recognition test were designed to be sensitive to complex associations, recognition too should be lost with pathological rapidity in patients over the ten-minute delay. This interpretation may be similar to what Eichenbaum et al.'s hypothesis would give for the effects of hippocampal lesions. Is this so? The patients we tested were only moderately amnesic because it would otherwise have been impossible to match their initial levels of explicit memory to that of their controls, but lesions were of several structures other than the hippocampus. The target article's hypothesis should predict that if amnesia is severe and caused by large parahippocampal lesions (unlike in our patients), then recognition as well as recall of single items should be lost with pathological rapidity over the ten minute period following learning, and that such amnesics should show faster loss of relational representations than amnesics with "downstream" hippocampal circuit lesions. Do the authors believe this?

The hippocampus: Relational processor or antiprocessor?

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Eichenbaum et al. have presented a well-reasoned case for relational processing as a key factor in the sensitivity of memory tasks to hippocampal lesions. They conclude that the hippocampus is itself a relational processor. However, their analysis arbitrarily excluded nonmemory tasks. Including these nonmemory tasks in the argument allows one to retain much of the analysis of relational processing, but would lead to the conclusion that the hippocampus is a device which *prevents* relational processing.

The authors' stated aim was "to present and support a hypothesis about the distinct and interactive memory functions" of the hippocampus and as a result they did "not consider . . . studies on orientation, distraction, exploration, motor patterns, operant schedules, emotion, and species-specific behaviors" (sect. 1.1). Probably for the same reason, they, like a number of other memory-oriented theorists, present a picture of the hippocampus as an appendage to the cortex with no recognition of the important contribution of septal input to hippocampal function (Gray 1982; Gray & McNaughton 1983; McNaughton 1991).

For Eichenbaum et al., therefore, tasks such as DRL (differential reinforcement of low rates) present a problem since, as they note "timing requires only the representation of an isolated stimulus event." They resolve this problem by an appeal to the use of episodic memory to complete the task, coupled with the claim that "episodic memories probably depend on a relational representation." Whatever the truth of this with respect to DRL, it is difficult to see how such episodic memory, or any other aspect of relational memory, can account for the fact that hippocampally lesioned rats can learn to run down a runway for food as well as controls, can, but they are severely impaired in extinction – when all that is needed is for them to stop running, surely an even simpler and less relational task than acquisition.

Let us instead start with the view prompted by the extinction result: that the hippocampus is a key node in a "behavioural inhibition system" (Gray 1982). This system is postulated to be crucial for the behavioural inhibition consequent on presentation of signals of punishment, signals of nonreward, and innate anxiety stimuli. Its outputs include not only behavioural inhibition but also increased arousal and attention. On this view, runway extinction and DRL both require the hippocampus to the extent that they involve conflict between competing alternatives (in this case responses), which are concurrently activated. The business of the hippocampus is to eliminate the incorrect alternatives.

Let us see how this inhibitory view of the hippocampus fares in the context of the view that relational processing is a key to sensitivity to hippocampal lesions – a view which seems well justified by Eichenbaum et al. Note first that Eichenbaum et al. see neocortical association areas as "the final repositories of long-term memory." On current views of cell assemblies this implies that all the connections required for multimodal relational processing are already present between areas of the neocortex before the hippocampus is called into play. We can also assume that the plasticity rules of the network are such that simple associations can be made without the hippocampus. Given this

combination of connections and plasticity, why is the hippocampus needed at all?

A network tuned to make simple associations on the basis of a simple Hebbian learning rule would be likely to make innumerable partial, incorrect associations when required to make relational associations. That is, faced with a problem which requires one specific relational solution, the network would be likely to produce, albeit in some cases at lower strength, additional incorrect solutions – akin to the case with stimulus saturation (e.g., B. McNaughton & Morris 1987). An essentially inhibitory role of the hippocampus, which increased the signal-to-noise ratio in the cortex, would solve this problem. The hippocampus would interact with the neocortex to inhibit the inappropriate, conflicting alternatives (in this case stimulus alternatives).

The view that the hippocampus is required to *prevent incorrect* relation formation makes predictions which are in many cases the same as the view that the hippocampus is required to *generate correct* relation formation. It is, thus, necessarily consistent with much of the data supporting the idea that the hippocampus is a relational processor. There are some important differences, however.

First, the inhibitory view of the hippocampus extends beyond relational processing and hence accommodates not only the memory data reviewed by Eichenbaum et al., but also the data on orientation, operant schedules, emotion, and so on, excluded by Eichenbaum et al. (Gray & McNaughton, in preparation).

Second, it accommodates the extensive similarities between the effects of anxiolytic drugs (which impair the control of hippocampal theta) and septal lesions with those of hippocampal lesions. It is noteworthy that the machinery postulated by Eichenbaum et al. (Fig. 1) is not supposed to require input from the septum.

Third, the inhibitory view accounts for the fact that in many tests of amnesics the observed errors are intrusions from previous tests. If the hippocampus were required for storage or retrieval of correct items, these intrusions would not be expected; if it were required to prevent storage or retrieval of incorrect items they would.

The inhibitory view is, in the memory domain, very close to the views of the hippocampus, discussed by Eichenbaum et al., which emphasise interference. It is also consistent with the idea, also discussed by Eichenbaum et al., that learning can involve a reduction in the spread of activation in the cortex as cell assemblies become more focussed and efficient. However, it should be noted that interference between response alternatives, which would also be resolved by the hippocampus, is probably better described as conflict (and could well involve subcortical structures). The hippocampus, then, can be viewed as a device which improves the resolution of conflict at many levels.

An inhibitory view of the hippocampus has two other advantages. First, it is more consistent with phylogeny than Eichenbaum et al.'s position. Second, it provides a coherent picture of cortical systems.

The hippocampus is clearly not a vestigial structure in primates, but neither is it large in relation to the cortex. As "archicortex," the hippocampus appears particularly important for less encephalised species. It seems unlikely that these would have greater need for relational processing than more encephalised species. On the other hand, behavioural inhibition, particularly as a means of dealing with potential as opposed to actual threats, is a function that such animals are likely to need.

According to Eichenbaum, short-term, working, and long-term memory are all functions of the cortex, but intermediate-term memory is not. By contrast, an inhibitory view of the hippocampus places all memory in the cortex and in the strengthening of cortical interconnections. The hippocampus then plays the role of a relational "antiprocessor," among the other roles which stem from its position as a central node of the behavioural inhibition system.

Neocortical memory traces

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In the Eichenbaum et al. model, the neocortex and parahippocampal region play complementary, time-limited roles in the storage of single perceptual events: short-term and intermediate-term memory, respectively. The authors cite work on the behavioral physiology of these regions to support the proposal that neocortical representations are briefer and more susceptible to interference than those in the parahippocampal region. As Eichenbaum et al. point out, drawing conclusions about data derived from different studies using different tasks is problematic. In our laboratory, we have begun to explore the contribution of various regions to memory by using the same tasks to examine neuronal activity in those regions. We have not found evidence for the difference in storage between the neocortex and the parahippocampal region predicted by the Eichenbaum et al. model.

The anterior-ventral portion of inferior temporal (IT) cortex, a region that includes both the perirhinal cortex (which is part of Eichenbaum et al.'s "parahippocampal region") and the medial portion of area TE was studied using a delayed matching-to-sample (DMS) task. We found that IT neurons gave weaker responses when a current stimulus matched the sample stimulus held in memory (Miller et al. 1991b; 1993). Eichenbaum et al. call this a "passive" representation. This effect occurred even when five stimuli and seven seconds (the maximum tested) intervened between the to-be-remembered sample stimulus and the matching stimulus. In another paradigm, we tested the responses of IT neurons to initially novel stimuli as those stimuli became familiar (Li et al. 1993; Miller et al. 1991b). Many neurons showed a waning of their visual response with increasing familiarity. This effect was able to bridge 152 intervening stimuli and 5 minutes (the maximum tested). This "familiarity effect" seems well within the domain of Eichenbaum et al.'s "intermediate-term memory," and it occurred after the animal had only seen the stimulus twice.

Eichenbaum et al. suggest that neocortical memory traces are particularly labile for areas distant from the parahippocampal region. Although most of our work has centered on anterior-ventral IT cortex, we recently tested, through recordings in area V4, whether neocortical neurons outside this region could retain memories (Miller et al., unpublished observation). We found that IT and V4 neurons exhibit similar mnemonic properties. Note that for both IT and V4 neurons these effects occur very early in the visually evoked response. This suggests that memory storage occurred in these areas rather than reflecting feedback from another structure. Thus, it appears that memory traces in the neocortex can be highly resistant to perceptual interference and can last for several minutes, even without the prerequisite "substantial experience" suggested by Eichenbaum et al.

Some memory effects of neocortical neurons disappeared between trials of DMS tasks. This was taken by Eichenbaum et al. as evidence of the lability of neocortical memory traces. This observation, however, is not pertinent to the proposal that the neurons are *incapable* of retaining long-lasting memories. In DMS tasks, animals are required to retain memories only for a single trial. Retaining memories across trials can cause a buildup of proactive interference, disrupting performance. Thus, the "resetting" of some memory traces between trials is more likely to be due to an active process that restricts the memory comparison to within a single trial, rather than an *inability* of the neurons to hold the memory across trials (Miller et al. 1993).

Another physiological phenomenon that has been proposed to mediate memory storage is elevated levels of activity in the retention intervals of DMS tasks. This "delay activity" is what

Eichenbaum et al. call an "active" representation. Neurons in both IT cortex and area V4 show delay activity. For both these areas, even one intervening stimulus disrupts the mnemonic information carried in the delay activity (Miller et al. 1993; also Miller et al., unpublished observation). However, neurons in another neocortical area, prefrontal cortex, exhibit delay activity that can withstand perceptual interference (Chelazzi et al. 1993). Thus, this type of memory representation is more robust for one neocortical area, prefrontal cortex, than it is for neurons in or near the parahippocampal region, which is the opposite of what is predicted by the Eichenbaum et al. model.

Psychological studies suggest the existence of "active" (volitional) and "passive" (automatic) types of memory. It is important to point out that Eichenbaum et al. use "active" and "passive" to refer to a physiological distinction that may not relate directly to active and passive types of memory. Indeed, recent data from our laboratory indicate that active and passive types of memory have correlates in the neocortex but do not simply correspond to the "active" and "passive" representations of Eichenbaum et al.

Reduced neural responsiveness appears to mediate the automatic (passive) judgments of stimulus recency that underlie the performance of standard DMS tasks. In situations where the animal must actively hold a specific stimulus "in mind," we have observed a third type of physiological effect, enhanced responding to matching stimuli (Chelazzi et al. 1993; Miller & Desimone 1994). We have so far observed this enhancement in both IT and prefrontal cortex; we do not know whether it occurs elsewhere. Since delay activity in IT cortex and area V4 is labile, it does not appear to mediate either passive or active retention across perceptual interference. However, delay activity in prefrontal cortex appears to mediate active holding of a stimulus "in mind" (Chelazzi et al. 1993). Thus, the relationship between neuronal activity and behaviorally defined memory is more complex than the "active" and "passive" physiological distinction.

It is difficult to draw strong conclusions about the physiological underpinnings of memory; the data are sparse and the relationship between the activity of single cells and behavior is complex. So far, we have not found any evidence for the model proposed by Eichenbaum et al. However, as we learn more about the localization of different types of mnemonic mechanisms and how they relate to behavior, we may find that the neocortex and parahippocampal regions differ for some of these mechanisms and not others.

Relational but not spatial memory: The task at hand

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Eichenbaum, Otto & Cohen propose that the hippocampal formation is critical for relational memory. Because all spatial memory tasks necessarily require relational memory, and because the spatial memory hypothesis of O'Keefe and Nadel (1978) is currently the predominant if not prevailing view of hippocampal function, the critical test to distinguish the present model from O'Keefe and Nadel's must be a test of nonspatial relational memory.

Conditional discriminations are a class of tasks that can be designed to examine nonspatial relational memory. For example, on a choice between "X" and "Y," "X" might be correct if the preceding cue was "A," but "Y" would be correct if the preceding cue was "B." Accurate performance on this kind of task cannot be based on a particular item's familiarity, novelty, reward history, or stimulus-response history; instead, choices must be based on the association of one stimulus with another (see D'Amato et al 1985 for discussion).

Eichenbaum et al. discuss the few studies of nonspatial conditional discrimination that have generated data consistent with their model, but they have neglected to discuss several other studies of this kind that argue against their model. For example, Murray et al. (1989) and Gaffan and Harrison (1989) provide several instances of conditional discriminations that are unaffected by fornix transection. In these studies, "places" in a test room served as the conditional cues, and it was likely that the "places" provided distinct visual cues that could be used to guide choice. Consequently, the lack of effect of fornix transection was interpreted as lack of critical involvement of this structure in (nonspatial) visual-visual conditional discriminations. Because these tasks admittedly used conditional cues that confounded spatial and visual features, I shall consider in detail only versions of conditional discriminations that are more evidently nonspatial.

To date, at least three sets of findings demonstrate that the hippocampal formation is not critical for stimulus-stimulus associations. First, Murray and Mishkin (1985) reported that monkeys with aspiration lesions of the hippocampal formation plus underlying parahippocampal cortex performed at high levels of accuracy on a tactual-to-visual delayed nonmatching-to-sample task. In this task, the monkey first touches and displaces a sample object in the dark, and then, using vision only, must avoid this object in favor of another at the subsequent choice test. Accurate performance presumably made use of the tactile-visual associations learned through the extensive training the monkeys had received with the stimulus objects, both tactually and visually, before and after their operations (Murray & Mishkin 1984).

Second, Murray et al. (1993) examined the ability of monkeys to learn visual-visual paired associates, a task in which one visual stimulus guided choice between two different visual stimuli that were presented a half second later. In this task, unlike the earlier one, the stimulus-stimulus associations were arbitrary, in that they did not derive from one object, and the association was tested in both directions (e.g., from "A" to "X" and from "X" to "A"). Here again, monkeys with aspiration lesions of the hippocampal formation plus underlying parahippocampal cortex retained preoperatively learned stimulus-stimulus associations almost perfectly, and learned new ones at a normal rate.

Finally, Bunsey and Eichenbaum (1993b) recently trained rats to perform an odor-odor conditional discrimination, one designed specifically to tax nonspatial relational memory. Rats with selective lesions of the hippocampus actually performed better than the controls, a finding that was not only *not* predicted, but argues against the hypothesis under consideration.

Eichenbaum et al. would no doubt invoke the idea that the monkeys and rats had learned the conditional discriminations described above by "fusing" the stimulus elements of a given pair into a single compound or "configural" stimulus (in the sense used by the authors in sect. 4.5), thereby precluding the need for relational memory.

But even if Eichenbaum et al. plead "fusion of stimulus elements" for the solution of these tasks by hippocampectomized animals, which on the face of it seems implausible for such a range of tasks and species, there is a difficulty with this position. In all three of the studies in question, not only did lesions of the hippocampal formation fail to disrupt performance, but lesions of adjacent medial temporal lobe structures did disrupt performance. The effective lesions were of the amygdala plus underlying cortex (the anterior portion of the ento- and perirhinal cortex, or rhinal cortex) in Murray and Mishkin (1985), and the rhinal cortex alone in Murray et al. (1993) and Bunsey and Eichenbaum (1993a). Because in their view the nonrelational process involving "fusion of stimulus elements" is independent of both the hippocampal formation, on the one hand, and the rhinal cortex plus parahippocampal cortex, on the other, lesions in either of these areas should fail to affect conditional discriminations learned in a nonrelational way.

Thus, Eichenbaum et al.'s model fails in either of two ways. If the conditional discriminations were taxing relational memory, the model cannot account for the failure of hippocampal lesions to disrupt performance on these tasks. Alternatively, if the conditional discriminations were taxing nonrelational memory, the model cannot account for the severe disruption of performance that follows rhinal cortex lesions.

In summary, the foregoing evidence weighs heavily against the idea that the hippocampal formation is critical for nonspatial stimulus-stimulus association. It is consistent instead with the idea that the rhinal cortex, but not the hippocampus, is critical for the kinds of nonspatial stimulus-stimulus associations being learned by monkeys and rats, and, therefore, for at least some kinds of nonspatial relational memory.

Hippocampus, space, and relations

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Eichenbaum, Otto & Cohen are to be commended for trying very hard to resolve the circularity that plagues declarative theory of memory. The circularity has been clear from the beginning: the precise properties of declarative memory were never spelled out. Its boundaries were defined instead by reference to the amnesic syndrome, which was characterized as a selective loss of declarative memory. Whatever was absent in amnesia was, by definition, part of declarative memory. The hippocampus played a central role in this story: damage to this structure is common in amnesia, and therefore it must be at the core of declarative memory (Squire 1992). By extension, declarative memory became what an animal (or human) lost if it had damage in the hippocampus. If an animal could perform without its hippocampus, performance was said to be based on something other than declarative memory. In all this, clear definitions of declarative memory were lacking, and that is the virtue of the target article by Eichenbaum et al. It attempts to specify just what declarative memory is and does. The fact that this attempt fails suggests that the idea of a single declarative memory system is not viable.

Theories about the function of the hippocampus have settled on the view that it is a selective memory system, but there remains a central dispute about how to characterize that selectivity. One view, first espoused by O'Keefe and Nadel (1978; Nadel & O'Keefe 1974) suggests that the hippocampus is selectively involved with memory for a certain kind of spatial relations, giving rise to internal representations akin to "cognitive maps." The alternative view, espoused in varied forms by various authors (e.g., Squire 1992), and most recently by Cohen, Eichenbaum and their colleagues, is that the hippocampus is a component of a selective, declarative, memory system concerned with storing information about "relationships among perceptually distinct items." In this view, the spatial relations emphasized by O'Keefe and Nadel are merely a good (perhaps the best) example of the more general class of relations the system is concerned with. One historical note is important here: Eichenbaum et al. (see also Cohen & Eichenbaum 1993) insist on referring to the cognitive map theory of hippocampal function as a "nonmemory" theory. The same misclassification has been made by other proponents of the declarative memory approach. One wonders how this can be, since O'Keefe and Nadel (1978) stated in their *very first paragraph* that "the hippocampus is the core of a neural memory system providing an objective spatial framework within which the items and events of an organism's experience are located and interrelated" (O'Keefe & Nadel 1978, p. 1). Although one can understand how such a statement, buried perhaps several hundred pages into a long and sometimes tedious monograph, might go unnoticed, it is hard to see why a clear statement at the very outset of our book has been turned on its head. Isn't it about time that this blatant mistake is excised from the literature, since it has only added to the confusion with which one approaches the functions of the hippocampus?

Recently, some of the data confusing the discussion of these different theories have been clarified (for my views on these developments see Nadel 1991; 1992; in press). In particular, the results from work with primates now show that the damage in the medial temporal region causing significant deficits in nonspatial tasks such as delayed nonmatching to sample (DNMS) resides outside the hippocampus itself, in areas such as perirhinal cortex and the parahippocampal gyrus (e.g., Zola-Morgan et al. 1989c). This has brought the primate literature into closer correspondence with the rodent literature, which has consistently emphasized the spatial nature of hippocampus functions. Whatever one eventually makes of the notion of declarative or explicit memory, it seems clear that it will be spread across a number of structures, and that these different structures will be contributing something different to the overall function. What remains to be determined is whether or not the very notion of declarative memory has any predictive or explanatory utility.

Exactly what is a declarative memory in terms of representation, according to Eichenbaum et al.? They emphasize the *relational* nature of declarative information, and the *distinctiveness* of the items that are being related in memory. The result of all this is representational flexibility and creativity, properties that were already associated with the hippocampus by O'Keefe and Nadel. Thus, it is not the properties of the system that are in dispute, but rather the way in which these properties arise.

Eichenbaum et al. (sect. 2) state that

> the hippocampal system subserves processing that involves comparing and relating . . . individual representations to other memory representations, creating relational representations according to the relevant contingencies between the items and the structure of any already established memory organization that involves those items.

Exactly what does this mean, and how can we use it to make experimental predictions? I cannot find clear answers to these critical questions in the article under discussion. The above definition sounds like a perfect description of a variety of learning paradigms in which animals (and humans) are subject to the relational contingencies between distinct stimuli, but in which damage to the hippocampus has no effect. Standard classical conditioning would seem to be such a case, though the authors argue that it is not. They say that the hippocampal system is not required for learning about the relations between particular responses and particular stimuli, but I cannot see how in their version of the declarative model, they can say this. Are responses not items that animals have to learn about? If not, why not? This reader, at least, is left not understanding what is meant by a declarative representation – I read the words, but I just don't get the meaning.

This lack of clarity at the heart of the declarative notion of representation is only part of the problem. Even more troubling is the fact that Eichenbaum et al. rely on the "temporal" properties of the declarative system to pick up the slack when the representational properties will not work. Thus, if a task looks as if it might require relational processing but no deficit is observed after appropriate lesions, the claim is that the temporal demands do not require the declarative system. On the other hand, if a deficit is observed in a task that does not appear on the face of it to involve relational processing, then the temporal demands are trotted out to account for the result. This is a most convenient if not particularly parsimonious way of building a theory. Attribute to a system two very different functions and then use them interchangeably (dare I say flexibly) to explain just about any result you want. It might be convenient, but it is neither predictive nor explanatory, since it is not possible to

state in advance when one, or the other, of the orthogonal functions of the declarative system are to be called into play. Consider, for example, Eichenbaum et al.'s explanation for the role of the hippocampus in timing (sect. 4.9). They note that the extant results seem "to call into question our contention that the hippocampal formation is not critical to memory for single isolated cues. However, one important consideration involves the nature of the event that is remembered over the timed interval and how this memory supports timing. Our view is that the remembered event in timing tasks *probably involves a relational rather than an individual representation.*" (emphasis mine). Creative this may be, but it hardly gets around the fundamental circularity at the heart of declarative theory: If there is a deficit, the task is declarative (relational); if there is no deficit, it is not. Eichenbaum et al. have added a new twist by including a temporal domain in their version of declarative theory, but this actually makes matters worse with regard to circularity, as the above example from their article indicates.

Eichenbaum et al. argue against the use of what they refer to as "psychoarithmetic," noting that there is a scientific rule that even a single example or counterexample can be important and must be explained. In a world of clean data, perfectly placed lesions, and well-specified theories this picture might apply, but that is not the world we inhabit. Instead, we must choose between theories that are more-or-less circularly defined, and sources of data that are more-or-less to the point. In the domain of hippocampal research, the facts are roughly these: damage to the hippocampus *always* causes learning deficits in a certain, well-defined kind of spatial task that we have called "place" learning. There are *no* exceptions to this statement except for tasks that others call place learning but that do not fit the definition we gave to that term (e.g., Eichenbaum et al. 1990). These few exceptions fall into the class of spatial tasks that can be solved by non-place strategies, and hence do not absolutely demand a functional hippocampus. On the other side, damage to the hippocampus *sometimes (in fact very rarely)* causes deficits in tasks that do not seem on the face of it to involve learning about places. Some of these exceptions have fallen away because further research has shown that learning about places ("contexts") is surreptitiously involved in tasks that had not been well understood before (e.g., Good & Honey 1991; Penick & Solomon 1991; see Nadel & Willner 1980; Nadel et al. 1985 for a thorough discussion of the role of the hippocampal place-learning system in context). Other exceptions remain, as challenges for the future.

We cannot readily apply the same binary logic to the declarative approach because what counts as declarative is just not well specified, as we have seen. Even so, there appear to be many counterexamples to the claim that declarative memory is involved with all kinds of relations. In one very important study, Douglas (1966) tested rhesus monkeys with lesions in the hippocampus on what is known as a "transposition" task. In this task, animals are trained in a discrimination which demands relational learning, such as the fact that the larger, or the darker, of the discriminanda will be rewarded; indeed, the transposition task was invented in the 1930s as a way of studying how animals learn about relations. Douglas showed that hippocampal damage had no effect on the ability of the animals to show transposition, hence no general effect on their ability to learn about relations. This appears on the face of it to be a very strong counterexample to the claim of a general relational defect; this kind of counterexample simply does not exist in the place learning literature.

The tack of adding a second function to the declarative system to account for some portion of these counterexamples is not very promising. It promises to return theorizing about the hippocampus to the days when "hypothesis drift" was the norm – theoretical terms changed their meaning with each new data point (see Nadel & O'Keefe 1974 for some discussion of this). If declarative theory is not to go the way of "response inhibition," "response braking" and "working memory," it is going to have to do a much better job of saying what it really means. It might start with a taxonomy of relations that fit into the definition of "declarative." It might then proceed to a systematic program of research on the role of the various parts of the hippocampal system that are involved in each such relation. Such a taxonomy will reveal that there are actually rather few kinds of relations; spatial (several kinds), temporal, causal, similarity, semantic, familial/social, and mathematical relations come to mind, and some of these might collapse into others. It is very likely that a different part of the brain is concerned with each one of these relations, and that the hippocampus is where places are at home.

Functional components of the hippocampal memory system: Implications for future learning and memory research in nonhuman primates

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Research on the neurology of learning and memory in nonhuman primates has progressed at a remarkable pace. In just over 15 years since Mishkin's landmark paper (Mishkin 1978), the consensus view has emerged that the hippocampus and closely associated cortical regions comprise the medial temporal lobe structures critical for normal declarative memory. Based on this background of information, and taken together with the substantial literature from studies of rats and humans, the field now seems poised to address a second generation of questions concerning the role of the hippocampal system in learning and memory. The target article outlines a specific hypothesis suggesting that individual components of the hippocampal system mediate distinct and dissociable memory-processing functions. This view represents a marked departure from other current lines of investigation that have emphasized quantitative, rather than qualitative, differences in the effects of damage to various components of the hippocampal system (e.g., Zola-Morgan et al. 1993). The merits of these alternative perspectives will be determined ultimately, of course, by direct, systematic investigation. Eichenbaum, Otto & Cohen's thoughtful exposition, however, suggests that a distinct shift in experimental approaches may be necessary to test current theories of hippocampal memory function. The purpose of the present commentary is to highlight the implications of this view for future learning and memory research in nonhuman primates.

A major aim of modern neuropsychological studies of learning and memory in monkeys has been to identify regions of the brain that, when damaged, cause deficits on standardized testing procedures such as the delayed nonmatching-to-sample (DNMS) task. Unfortunately, considerably less attention has been directed at understanding the basic processes that support normal task performance in intact animals, or toward defining the nature of memory representations that support residual behavioral capacities in subjects with hippocampal system damage. The importance of this issue for testing current theories of hippocampal function has become increasingly clear in recent years. Data reviewed here by Eichenbaum et al. for example, indicate that selective damage to the hippocampus or its connections via the fornix causes little or no impairment in monkeys as assessed by a variety of widely used amnesia-sensitive tasks. These results lead to the surprising conclusion that, among the medial temporal lobe structures known to be critical for normal memory, the hippocampus itself makes only a minor contribution (e.g., Alvarez-Royo et al. 1993a; O'Boyle et al. 1993; but see

Beason-Held et al. 1993). This interpretation, however, is complicated by the fact that standard testing procedures may fail to reveal differences in the specific nature of the memory representations supporting performance in intact subjects versus monkeys with hippocampal damage.

Preliminary findings in rats, for example, suggest that nonhippocampal mnemonic capacities can have ameliorative, or even facilitatory effects, on task performance. In these investigations, rats were tested on tasks specifically designed to parallel amnesia-sensitive procedures (i.e., DNMS and paired-associate learning) used commonly in monkey and human research. The surprising result was that performance in animals with selective damage to the hippocampus was actually improved relative to control levels (Bunsey & Eichenbaum 1993b; Wilner et al. 1993). In the most general sense, these results are consistent with the idea that the hippocampus contributes in some way to DNMS and paired-associated performance. The more salient issue in the present context, however, is that standard behavioral measures in many learning and memory tasks designed for monkeys, whether they reveal robust impairments, no change, or improvements as a consequence of a given experimental manipulation, may provide relatively little insight into the nature of mnemonic processes supporting performance. Thus, as the focus of attention in nonhuman primate research moves away from identifying the regions of the brain that participate in learning and memory, and shifts more toward asking questions about the specific functions mediated by these systems, increasing effort will need to be directed toward understanding the basic psychological processes underlying performance in tests of learning and memory.

Designing appropriate behavioral procedures to directly and systematically evaluate Eichenbaum et al.'s hypothesis in nonhuman primates will undoubtedly prove challenging. New tasks are needed in which it can be empirically determined that performance in intact subjects is supported by relational representations and the flexible utilization of relational memory organizations. Equally important, in cases where monkeys with hippocampal system damage achieve normal, or even superior, quantitative levels of learning, the proposal requires direct confirmation that the form of representation supporting performance is fundamentally nonrelational and inflexible. Robust deficits resulting from hippocampal damage should also be evident across multiple testing procedures that place equivalent demands on relational representation and representational flexibility, independent of the nature or category of the stimulus materials used to examine learning and memory. Achieving these aims will require a level of refinement in behavioral assessment only rarely realized in nonhuman primate studies. Ultimately, then, perhaps the value of Eichenbaum et al.'s proposal should be judged less by whether its specific predictions prove valid, and more by its success in prompting the development of new behavioral tools necessary to advance the study of hippocampal learning and memory in nonhuman primates.

Does it still make sense to develop a declarative memory theory of hippocampal function?

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Eichenbaum et al.'s target article is an expanded account of the declarative memory theory of hippocampal function (Cohen & Squire 1980). The new account explicitly addresses the spatial deficits so widely reported to result from hippocampal dysfunction (for review see Nadel 1991) while at the same time attempting to account for data on temporal factors (Rawlins 1985), all within an essentially nonspatial theory. This is an ambitious enterprise, whose grand aim of integrating spatial and nonspatial data within a single theoretical framework is also very much an interest of our own (Lyford et al. 1993; Rawlins et al. 1991; Rawlins et al. 1993). Given that we agree with the goal, what of the specific route whereby the target article tries to attain it? Our commentary first considers the overall theoretical approach and then presents data from experiments whose outcomes bear on some of the issues raised.

The theory largely depends upon Eichenbaum et al.'s attempt to characterize specific components of normal memory capacity and identify them with specific brain regions. The physical partition of temporal and relational memory components permits the authors to use components of the temporary memory buffer theory (Marr 1971; Rawlins 1985) while themselves remaining buffered from some of its admitted shortcomings (e.g., Rasmussen et al. 1989; Rawlins et al. 1993). Likewise, it can address the spatial memory deficit so often reported in rats without as a result being confined simply to the spatial domain. In these respects it accurately captures an *operational* aspect of the effects of hippocampectomy: if you want to see a big hippocampal lesion effect, use a spatial working memory task (thereby combining time, space, and the need for flexibility).

Does it actually deliver much more than a restatement of operational truths of this kind? We are not yet convinced that it does. One indication of this lies in the difficulty of knowing whether or not a specific task (or task version) actually requires the use of relational information, and thus depends upon hippocampal function. Eichenbaum et al. are of course aware of this kind of problem: the final paragraph of section 1 acknowledges the danger of circularity in using neuropsychological findings to define the hippocampal system. In human experiments, verbal commentary can enable us to identify declarative memory: animals cannot make such comments, and so we cannot directly demonstrate their use of declarative memories. But how easily can we control or demonstrate their use of relational memories? Whereas temporal contiguity can be varied parametrically, the need to use relational content is much harder to control, or even identify. At a number of points in the target article the authors appear to suggest that particular tasks (or task variants) must require memory for relationships between stimuli because hippocampal damage leads to a deficit on those tasks (e.g., sects. 4.5.2, 4.6, 4.9, and 4.10). This sounds as though the data are being required to conform to the requirements of the theory, rather than the other way round. If the tail is not to wag the dog too vigorously, we need explicit behavioural tests to allow us to decide whether or not particular tasks require normal animals to use memory for relational information.

What is the independent evidence for relational learning in animals? One line of evidence originates in Eichenbaum and colleagues' earlier work on olfactory learning (see sect. 4.2). The critical issue concerns the disruptive effects of recombining individual elements from prior simultaneous discriminations: if animals had learnt the relationship between the elements then recombination should lead to impaired performance. This effect was seen only in animals with fornix lesions. Reid and Morris (1993) point out that this is paradoxical: such an impairment should be seen only in animals that have formed relational associations; the current theory suggests that these should have been the controls, rather than the animals with lesions.

It is possible that clearer results could be obtained using visual/tactile stimuli, because the individual elements do not physically interact with one another, thus ensuring that any configural learning of a relationship between elements has a psychological rather than a physical basis. It is therefore interesting that in discrimination learning, animals typically learn absolute rather than relational associations, although certain designs can promote the latter (Mackintosh 1974, pp. 543–619).

It has been suggested (sect. 3.1) that using concurrent rather than sequential discrimination learning procedures would emphasise the need for relational learning.

We have examined the effects of hippocampal removal in a number of object learning tasks in which Eichenbaum et al. would expect relational processing to occur, and have so far found (1) that normal rats perform these nonrelationally, and (2), consistent with Eichenbaum et al.'s view, hippocampal impairment did not occur. Thus hippocampectomy did not selectively disrupt performance when the memory load was increased by two-, five- or six-pair concurrents, nor when positive and negative stimuli were randomly paired in the two-pair case during acquisition itself, nor when stimuli were randomly paired after acquisition in any experiment. Furthermore, hippocampal rats completed configural tasks either when the significance of a pair of objects presented together was opposite to that of either object presented alone, or when only the spatial relations between a given set of objects determined their significance. Presumably such tasks can be learned as individual representations of composite cues; such an account of the data would be inconsistent with Sutherland and Rudy's (1989) configural theory, but consistent with the view that when learning is not relational, there will not be a hippocampal lesion effect (target article). But these results also show how hard it is to devise experimental tests that necessarily entail relational learning for their solution. Not until we can do this can we consider whether the role of the hippocampal system in the relational aspects of nonspatial tasks is basically the same as in spatial tasks. Our difficulty lies not in knowing what should happen if relational learning *does* occur, but rather in knowing when it *will* occur.

Finally, we should draw attention to two specific failures of Eichenbaum et al.'s proposal. First, we have already reported that the impairment of nonspatial delayed matching to sample (DMS) caused by hippocampal dysfunction depends critically upon the physical nature of the stimuli used, rather than only on whether or not stimuli are repeatedly presented. This is seen after hippocampal aspiration lesions or fornicotomy (Rawlins et al. 1993), intraventricular AP5 infusion (Lyford et al. 1993) or medial septal lesions, but not cytotoxic entorhinal lesions (Yee & Rawlins, in preparation), and this is unaccounted for by the present theory. Second, we find that cytotoxic entorhinal lesions do not impair rats' performance of nonspatial DMS, even under conditions of high interference (Yee & Rawlins, in preparation). This suggests that the contribution of the parahippocampal region to such tasks may require further investigation.

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From Heisenberg's cat to Eichenbaum's rat: Uncertainty in predicting the neural requirements for animal behavior

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The relational memory theory (RMT) by Eichenbaum, Otto & Cohen is an important and comprehensive integration of data that provides a new perspective on the neuropsychology of memory. The inclusiveness of the theory makes it, for me, the most appealing of the current descriptions of memory and brain. The emphasis on the fact that many memory tasks can be solved using more than one strategy, and hence more than one neural and cognitive system, is crucial for continuing progress in the analysis of memory and brain. Following the strategy suggested by the theory, I will suggest below where some alternative or additional views may be helpful in this effort.

Uncertainty in predicting lesion effects. Perhaps the most important methodological contribution of the target article is its emphasis on the multiple solutions available for most tasks, and the importance of probe tests for revealing the strategies and memory systems actually used by individual animals. Although other multiple memory theories have recognized that animals can use multiple strategies and memory systems to solve tasks (e.g., Hirsh 1974; O'Keefe & Nadel 1978; Olton et al. 1979), the other theories have emphasized task categories aimed to force animals to use one or another strategy, and they use these categorical distinctions to reveal the brain systems required for a given task. The RMT argues that parametric manipulations within the usual task categories (e.g., spatial memory, working memory, etc.) can produce different outcomes in normal and brain-damaged animals. The RMT theory argues in particular that these parametric manipulations encourage either a relational or an individual memory strategy. On reexamination, this view may help integrate the apparent discrepancies in the memory literature.

A recent experiment by White and McDonald (1993) at McGill demonstrates the truth of this uncertainty in normal animals. Rats were trained to swim to a visible platform in the Morris maze for three days. The platform was hidden for a fourth day of training, and the same four day regimen was repeated. After the two blocks of training, the visible platform was moved to a new location. The first trial of testing with the new location provided the important probe test for the memory system and learning strategy used by the normal rats. Four of the eight rats swam directly to the visible platform in the new location, demonstrating that they used a nonspatial strategy. The other four rats swam first to the former platform location, demonstrating that they used a spatial strategy. Thus, a task that allowed two strategies was performed, and each strategy was used by half of the group of rats. Predicting the effects of brain lesions (especially those made after training and the adoption of a successful strategy) will have to directly test the strategies available to the animals.

Relational representations. The most appealing aspect of RMT is its inclusiveness. The RMT account of the declarative, spatial, configural, and working memory deficits is consistent with evidence from amnesic patients with temporal lobe damage, as well as from other animals with homologous lesions. The difficulty with RMT concerns defining the relationships that are unique to relational representations. The authors do not provide explicit definitions or principles for defining other relationships that should require encoding by the hippocampal system. For example, spatial representations include several well-defined relationships, such as distance, angle, direction, and size among distal stimuli. Eichenbaum et al. should provide some heuristics for defining the other types of relationships that require the hippocampal system. Flexibility is one principle cited to distinguish relational representations from others. Indeed, inflexible, predictive relationships or contingencies, for example, the stimulus-reward or stimulus-response relationships that define classical and operant conditioning tasks, are not impaired by hippocampal system lesions. However, the brain together *with* the hippocampal system intact cannot perform simple association tasks such as conditioned cue-preference tasks, which are impaired by amygdaloid lesions, or cue-approach tasks such as the visible platform task in the water maze, which are impaired by caudate nucleus lesions (e.g., White & McDonald 1994). Inflexible relationships among stimuli are crucial to these types of tasks, and the theory needs to explain why inflexible relationships are not remembered by the hippocampal system. Without these specifications, disconfirming the RMT will be difficult. The flexibility principle is important, but it also needs to be

specified more clearly at the level of representation and processing for the same reasons.

Intermediate-term memory. The RMT proposes that declarative memory is processed in two sequential stages by two components of the hippocampal system. Eichenbaum et al. propose that the hippocampal system is needed to maintain individual representations in intermediate-term memory (ITM), a longer period than that typically described for short-term memory (STM), and that the parahippocampal region is necessary for this ITM storage of both individual and relational representations. In contrast, it is proposed that the hippocampal formation is required for maintaining relational representations in ITM, as well as for the rapid acquisition of long-term memory (LTM). Clearly, information persists in the central nervous system for varying intervals, and thus many memories can, and perhaps should, be distinguished (e.g., Lynch & Granger 1992). However, defining separate systems is more difficult, and a more fruitful approach may be to adopt a consolidation view in which different brain regions have different probabilities, rates, sizes, and durations of synaptic strength changes along with distinct architectures for representing and processing specific types of information. Parsimony and the variance accounted for by these different views will determine their utility. Finally, the data used to support this distinction compare lesions of the fornix or neurotoxic lesions of the hippocampal formation with lesions of the parahippocampal region. Further comparisons between fornix lesions and parahippocampal lesions are needed, however, because fornix lesions reduce AChE (acetylcholinEsterase) staining and theta rhythm recorded from the entorhinal cortex (Mitchell et al. 1982), and would be expected to disrupt some aspects of entorhinal cortical function.

Other issues. The explanation of trace conditioning relies on a physiological and anatomical argument rather than a representation/processing argument. The explanation may well be correct, but it points to a missing component to the theory – a computational level of analysis that would link cognitive and neural descriptions of learning, representation, and processing. This perspective would require pharmacological and neural architectural data to be included with the anatomical and physiological data already constraining the theory. These levels of description are needed if RMT is to fulfill its promise as a comprehensive explanation of memory and amnesia.

What are the best strategies for understanding hippocampal function?

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The hippocampus holds two very prominent positions in behavioral neuroscience: (1) it has been the subject of more research and theoretical speculation than any other brain area, and (2) it is the brain area that engenders the highest level of disagreement concerning function. Although we have known since the pioneering work of Scoville and Milner (1957) that the hippocampus is involved in learning and memory, this generalization may be the extent of the agreement on the functions of this structure. Eichenbaum, Otto & Cohen have made the most recent attempt at arriving at a parsimonious theory of the role of the hippocampus in learning and memory. To accomplish this, they have surveyed an enormous body of literature and have arrived at a view that attempts to account for the divergence of research on this structure. To oversimplify, in order to account for the largest portion of the data, they have combined the two basic tenets of most contemporary theories of hippocampal function: limited temporal storage of memories (e.g., Rawlins 1985; Scoville & Milner 1957) and storage of only certain types of memories (e.g., Squire & Zola-Morgan 1991). Of course, although this theory can in retrospect account for the data they present, the final judgment will await experiments designed to test their specific hypotheses. There may be a more fundamental problem for this type of theory, however.

Eichenbaum et al.'s approach is typically used in the study of brain-behavior relationships: select a single neural system or structure and then study the effects of various manipulations of this system or structure on behavior in a wide variety of paradigms and preparations. This is followed by an attempt to infer the role of this structure or system in behavioral and cognitive processes. Using this approach, Eichenbaum et al. have done an admirable job of synthesizing the relevant information and arriving at a tenable and testable hypothesis. We suggest, however, that although they have made good use of the "one structure multibehavior" approach, this may not be the most efficacious in producing meaningful information about brain-behavior relationships.

The potential pitfalls of the one structure multibehavior approach fall into two general categories. First, the behaviors considered are often not well characterized. Certain behavioral tasks may be considered to measure declarative memory and others place memory, and in some instances there are converging data to suggest that these assumptions are correct. In too many instances, however, assumptions must be made about experiments that use a new behavioral paradigm or a modification of an existing behavioral paradigm for which there is little information. Moreover, divergent behavioral paradigms are often considered to measure a single attribute (e.g., context). Again, beyond face validity, it is not clear that these paradigms measure what they purport to measure. A second issue revolves around considering neural structures or systems in isolation. Lesions to a single area, for example, almost certainly have influences in other areas in ways that are often unpredictable. Not considering these interactions can lead to erroneous conclusions.

In an attempt to address these issues, a number of researchers have adopted the model systems approach to learning and memory: Study a single, well-characterized behavior and determine the interactive contributions of a wide variety of (preferably all) neural systems to this behavior. The most widely used model system for the study of learning and memory is classical eyeblink (EB) conditioning in humans and rabbits. The ultimate goal of the model systems approach is to fully charactertize the neural basis, from systems to mechanisms, of a single type of learned behavior.

Using the model systems approach, considerable progress has been made in characterizing the neurobiological basis of learning in invertebrate (e.g., Kandel & Schwartz 1982) and mammalian (Thompson 1986) species, and more recently in beginning to understand how age-related memory disorders may be characterized (e.g., Solomon & Pendlebury 1992). A well-characterized behavior is used: classical conditioning, about which we know more than any other type of learning. Moreover, because of the prominence of the hippocampus in learning and memory, considerable attention has been devoted to characterizing the role of this structure in the conditioned EB response. It is these studies that suggest that the role of the hippocampus in learning and memory may not be fully characterized by the one structure multibehavior approach.

The one structure multibehavior approach relies heavily upon the effects of hippocampal lesions. By this logic, if lesions have no effect, then the hippocampus is not contributing to the behavior, and this category of behavior need not be included in the "functions" of the hippocampus. This may not be a valid assumption. For example, data from rabbit EB conditioning indicates that although the hippocampus is not necessary for the acquisition of the conditioned response (CR) – that is, lesions do not affect the acquisition process – subsequent studies have shown that other manipulations of the hippocampus that affect

its neuronal activity (e.g., scopolamine administration; Solomon et al. 1983) do disrupt conditioning. Moreover, this disruption may be through hippocampal interactions with the cerebellum, a structure necessary for the acquisition of the CR (Thompson 1986). To further complicate matters, related studies have shown that the patterns of conditioning-related electrophysiological activity in the hippocampus are affected by cerebellar activity (Clark 1984), suggesting that learning-mediated hippocampal activity may in turn be influenced by learning-dependent activity in other brain areas. It is this potentially important type of interaction that can be missed with the one structure multibehavior approach.

A second assumption of the one structure multibehavior approach is that there is stability across the life of an "engram." That is, the hippocampus plays a similar role in implicated types of learning and memory over time. Again, data from model systems suggest that this may not be a valid assumption. For example, Yang and Xiang (1988) have shown that intrahippocampal injection of the cholinergic receptor blocker QNB abolishes learned activity recorded from the cerebellum in animals early in the course of conditioning, but has no effect once the learned response is well established. Similarly, we have shown that more complex forms of conditioning, such as trace conditioning (Solomon et al. 1986), are disrupted following hippocampal lesions; and Thompson's group has recently shown that pharmacological manipulation of the hippocampus impairs retention of the trace-conditioned response in a time-dependent manner (Tocco et al. 1993). Eichenbaum et al. certainly discuss temporally limited memories, but it is not necessarily this type of temporal limitations to which their model refers.

In summary, Eichenbaum et al. propose a novel and testable hypothesis. This is an ambitious and important undertaking. We do not dispute a priori their views or hypotheses, but we question whether their general approach is capable of capturing the potential richness of function of the hippocampus, or of brain-behavior relationships in general.

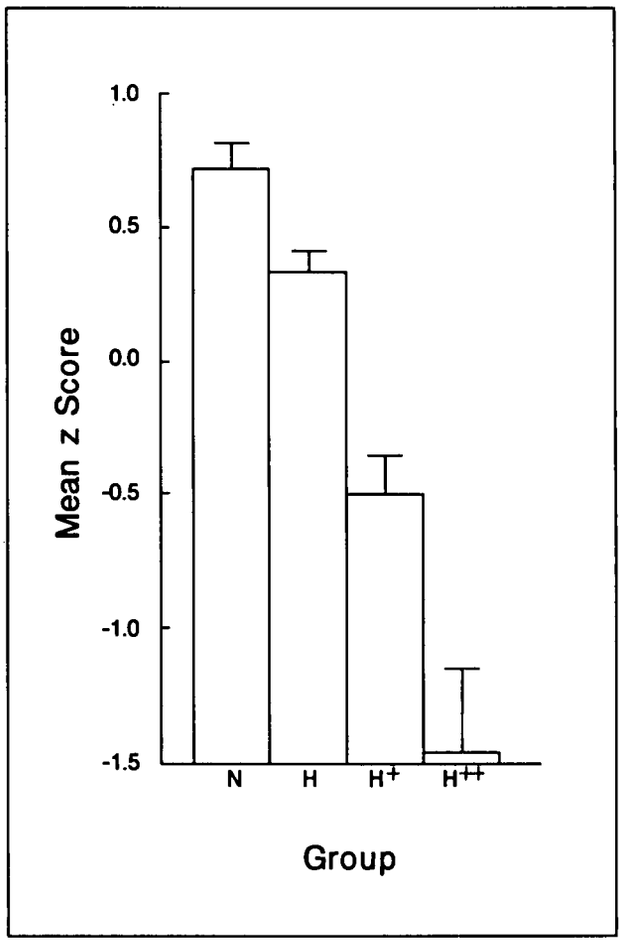

Figure 1 (Squire et al.). Mean *z* scores based on data from four measures of memory taken from two different tasks (delayed nonmatching-to-sample and delayed retention of object discriminations). N=10 normal monkeys; H=8 monkeys with damage limited to the hippocampus proper, the dentate gyrus, and the subicular complex; H^+=8 monkeys with damage that also included the adjacent entorhinal and parahippocampal cortices; and H^{++}=4 monkeys in which the H^+ lesion was extended forward to include the anterior entorhinal cortex and the perirhinal cortex. As more components of the medial temporal lobe memory system were included in the lesion, the severity of memory impairment increased. All between-group comparisons were statistically significant. Error bars indicate standard errors of the means. From Zola-Morgan et al., in press.

Functional distinctions within the medial temporal lobe memory system: What is the evidence?

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During the past several years, Eichenbaum's laboratory has carried out important work concerning the role of the hippocampus and related structures in declarative memory. In the authors' terminology, which we use here for clarity, the *hippocampal formation* includes the hippocampus proper, the dentate gyrus, the subiculum, and the fornix; the *parahippocampal region* includes the perirhinal, entorhinal, and parahippocampal cortices. The hippicampal formation and the parahippocampal region are the two major components of the *hippocampal system*. (For a critique of this terminology, see Suzuki's commentary, this issue). In their target article, the authors advance the idea that the hippocampal formation makes a qualitatively different contribution to declarative memory than the parahippocampal region.

Eichenbaum et al.'s proposal builds in part on recent findings in monkeys that point to the importance for memory function of the cortical regions adjacent to the hippocampal formation. Bilateral lesions limited to the hippocampus proper, the dentate gyrus, and the subicular complex cause significant memory impairment, but the severity of impairment is considerably greater when the damage also includes the adjacent cortical regions, that is, the perirhinal, entorhinal, and parahippocampal cortices (Squire & Zola-Morgan 1991). In addition, studies in monkeys (Gaffan & Murray 1992; Meunier et al. 1993; Suzuki et al. 1993; Zola-Morgan 1989c) and rats (Otto & Eichenbaum 1992a) show that lesions limited to the cortical regions themselves also cause severe memory impairment. The findings in monkeys suggest that the severity of memory impairment depends on the extent of damage within the medial temporal lobe memory system (Zola-Morgan et al., in press. Fig. 1). These findings also provide a way to understand why the amnesic patient H.M., who has extensive medial temporal lobe damage (Scoville & Milner 1957), is more severely amnesic than patient R.B., whose damage was limited to the CA1 region of the hippocampus (Zola-Morgan et al. 1986).

The proposal in the target article is that the parahippocampal region supports intermediate-term storage of individual items in memory, and the hippocampal formation mediates the pro-

cessing needed to form relational representations that permit comparisons among items and the flexible use of stored knowledge. This view leads to some straightforward predictions. Lesions of the parrahippocampal region should impair both intermediate-term storage and relational processing because, according to Eichenbaum et al., intermediate-terms storage is a prerequisite for a relational memory representation (damage to the parahippocampal region interrupts cortical inputs to the hippocampal formation). Thus, any memory task that includes a substantial requirement for retaining information for a few minutes, like delayed nonmatching-to-sample, should be severely impaired by parahippocampal lesions. In addition, even if a task requires only a little relational processing (it is difficult to know from the target article when a task requires relational processing), some impairment should also result from hippocampal formation lesions. Exactly this pattern of results has been reported for the delayed nonmatching-to-sample task in rats (Fig. 2, target article) and monkeys (Squire & Zola-Morgan 1991; Fig. 1). The difficulty is that this pattern of results is also easily accommodated by a single-function view whereby declarative memory function depends on all the structures of the hippocampal system. More complete damage to the system produces more severe memory impairment. The cortical areas adjacent to the hippocampal formation play a more important role in declarative memory than the hippocampal formation itself.

A potentially more telling prediction is possible in the case of tasks that depend substantially on relational processing. At the heart of the prediction is the idea that the relationship between the site of the lesion and the severity of impairment should be different for relational memory tasks than in the case of tasks that depend substantially on intermediate-term storage. Specifically, for relational memory tasks, lesions limited to the hippocampal formation should produce an impairment at least as severe as the one produced by parahippocampal lesions. Moreover, adding a parahippocampal lesion to a hippocampal formation lesion should not appreciably exacerbate the deficit, because the hippocampal formation lesion has already produced a complete loss of the function in question. Accordingly, a straightforward test of the present proposal is to compare directly the effects on relational memory of hippocampal formation lesions with the effects of complete lesions of the hippocampal system (i.e., a conjoint lesion of both the hippocampal formation and the parahippocampal region). To construct a decisive test, one would ideally compare the performance of two lesion groups (hippocampal formation vs. hippocampal formation plus parahippocampal cortex) on a relational (perhaps spatial) memory task across a range of task difficulty. The question of interest is whether the two lesion groups do or do not exhibit a similar relationship between task difficulty and memory performance. It should be noted that the finding of similar levels of impairment following fornix lesions and lesions of entorhinal cortex (Jarrard, 1986; Olton et al. 1978) is not helpful, because the entorhinal cortex comprises only a portion of the parahippocampal region.

With the emphasis for many years having been placed on the function of the hippocampal formation, it is easy to be impressed by the fact that lesions in the adjacent cortex also have a large effect on declarative memory. Eichenbaum et al. attempt to define separate functions for the hippocampal formation and the adjacent cortex and they predict that the impairment on some tasks should not be exacerbated by increasing the extent of damage beyond the hippocampal formation to include the parahippocampal region. At the very least, they predict that the impairment on some memory tasks as a function of lesion site should be strikingly different from the impairment-lesion relationship illustrated in Figure 1.

It is also important to note that Eichenbaum et al.'s view would require that, for some aspects of memory function, the severely amnesic patient H.M. should be no more impaired than amnesic patient R.B. Yet, after four decades of neuropsychological testing, it appears to most observers that H.M. is simply more profoundly amnesic across all declarative memory tasks than other amnesic patients, including patient R.B. For example, H.M.'s IQ-MQ (memory quotient) difference score is 43.7 (average of six tests, 1955 to 1983, Corkin 1984), whereas amnesic study populations typically have IQ-MQ difference scores averaging 20-30 points (Zola-Morgan et al. 1986). (Until these tests were revised in the 1980s, the IQ-MQ difference score was a common measure of the severity of memory impairment.) It seems unlikely that there is some aspect of memory, undetected over the years, that is no more impaired in H.M. than in other amnesic patients.

The anatomy of the medial temporal lobe is entirely consistent with the possibility that different parts of the system make qualitatively different contributions to declarative memory. Indeed, as discussed elsewhere (Suzuki et al. 1993), the perirhinal and parahippocampal cortices receive different complements of cortical inputs such that these cortical areas might be involved preferentially in visual memory and spatial memory functions, respectively. Although it is plausible that other functional distinctions apply within the hippocampal system, at present there is no evidence for this idea.

What can neuroanatomy tell us about the functional components of the hippocampal memory system?

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Over the last ten years, substantial progress has been made in our understanding of the connectivity of structures comprising the hippocampal memory system, particularly in the nonhuman primate. Indeed, our current understanding of the connectivity of the monkey entorhinal, perirhinal, and parahippocampal cortices (Fig. 1) provides the basis for some specific hypotheses concerning how these areas may contribute to memory function. First, from a neuroanatomical perspective, the entorhinal cortex, included by Eichenbaum, Otto & Cohen in the "parahippocampal region," has a number of unique connectional characteristics that (1) distinguish it from the perirhinal and parahippocampal cortices and (2) suggest that it may be more closely associated with the hippocampal formation. Second, recent neuroanatomical studies demonstrating differential cortical inputs to the monkey perirhinal and parahippocampal cortices suggest that these two areas may contribute in different ways to memory function. In the following commentary, I will describe the major connectional characteristics that distinguish the monkey entorhinal, perirhinal, and parahippocampal cortices and will suggest what these differential connections may tell us about their respective contributions to memory function.

A major distinguishing characteristic of the entorhinal cortex in both the monkey and the rat is that the cells of layer II provide a massive projection to the dentate gyrus. The entorhinal cortex also provides strong projections to areas CA3 and CA2, and has reciprocal projections with area CA1 and the subiculum. The powerful interconnections between the entorhinal cortex and the hippocampal formation suggest that these areas may also have strong functional interactions.

Another distinguishing characteristic of the monkey entorhinal cortex is that, except for the direct projection from the olfactory bulb, this structure receives inputs exclusively from higher-order polymodal associational areas, including prominent projections from the perirhinal and parahippocampal cortices (Insausti et al. 1987). In contrast, the perirhinal and

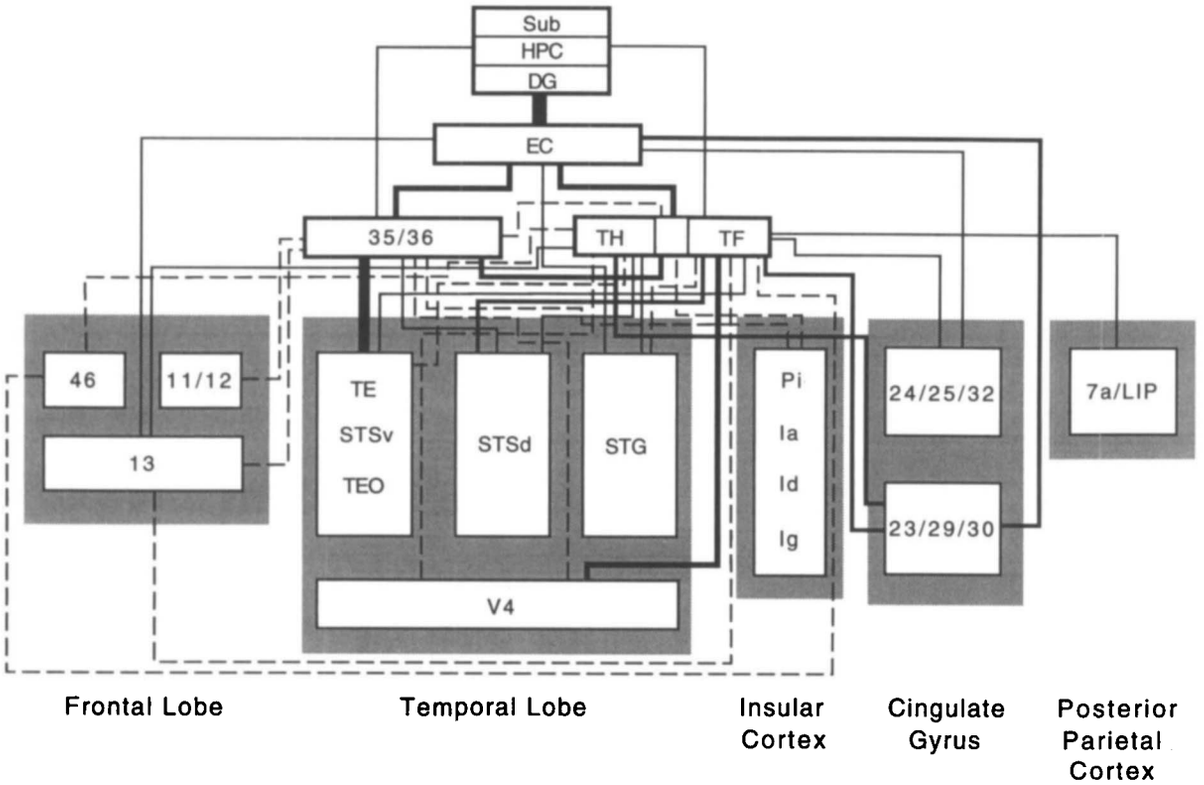

Figure 1 (Suzuki). Schematic diagram of the organization of cortical inputs to the monkey hippocampal formation (dentate gyrus, hippocampus proper, and subicular complex), entorhinal, perirhinal (areas 35 and 36), and parahippocampal (areas TH and TF) cortices. The thickness of the lines represents the relative strength of cortical input to the respective areas. The dashed lines represent inputs comprising less than 5% of all the direct cortical inputs to that area. The hippocampal formation receives its major cortical input from the entorhinal cortex. The entorhinal cortex, in turn, receives approximately two-thirds of its cortical input from the surrounding perirhinal (areas 35 and 36) and parahippocampal (areas TH and TF) cortices. The latter cortical areas receive widespread inputs from distinct subsets of unimodal and polymodal associational areas. Quantitative data used for this figure were taken from Insausti et al. (1987) and Suzuki & Amaral (1994). Other abbreviations: DG, dentate gyrus; EC, entorhinal cortex; HPC, hippocampus; Ia, agranular insula; Id, dysgranular insula; Ig, granular insula; Pi, parainsular cortex; STSd, dorsal bank of the superior temporal sulcus; STSv, ventral bank of the superior temporal sulcus; STG, superior temporal gyrus.

parahippocampal cortices receive much of their sensory input from higher-order unimodal associational cortices as well as polymodal associational areas (Suzuki & Amaral 1994). These projection patterns suggest that the entorhinal cortex is situated at a "higher level" of processing than the perirhinal and parahippocampal cortices.

Consistent with the idea that the entorhinal cortex is functionally more related to the hippocampal formation than to the surrounding cortical areas is the finding that monkeys with bilateral lesions limited to the entorhinal cortex exhibit only a mild memory deficit on the delayed nonmatching-to-sample (DNMS) task (Leonard et al. 1993; Meunier et al. 1993). The magnitude of their deficit resembles the mild deficit observed on this task after lesions limited to the hippocampal region (Alvarez-Royo et al. 1993b) or ischemic damage to the hippocampus (Zola-Morgan et al. 1992). In contrast, bilateral lesions limited to the perirhinal and parahippocampal cortices produce a severe impairment on the DNMS task (Suzuki et al. 1993; Zola-Morgan et al. 1989c). These behavioral and neuroanatomical data, taken together, support the idea that the entorhinal cortex is functionally more related to the hippocampal formation than the perirhinal and parahippocampal cortices.

While the monkey perirhinal and parahippocampal cortices share the common characteristic of providing prominent projections to the entorhinal cortex, recent neuroanatomical studies have revealed that the monkey perirhinal and parahippocampal cortices receive distinctly different kinds of cortical inputs (Suzuki & Amaral 1994). The monkey perirhinal cortex receives its strongest input from unimodal visual areas TE and TEO as well as strong input from the parahippocampal cortex. In contrast, the parahippocampal cortex receives strong projections from polymodal areas, including the retrosplenial cortex, the cortex of the dorsal bank of the superior temporal sulcus (STS) posterior parietal areas 7a and LIP, as well as visual areas VTF and V4. These anatomical data, together with the finding that bilateral lesions of the perirhinal and parahippocampal cortices produce an enduring and multimodal memory impairment (Suzuki et al. 1993), suggest that these cortical areas may play different roles in memory function. The perirhinal cortex may be particularly involved in visual object memory via its strong projections from visual areas TE and TEO. The parahippocampal cortex may be particularly involved in visuospatial memory via its strong projections from retrosplenial cortex and posterior parietal cortex. Whether these areas are involved in only the intermediate-term memory for object and spatial memory function, respectively, as suggested by Eichenbaum et al., or they have more complicated functional interactions with the entorhinal cortex and hippocampal formation, cannot be determined on purely neuroanatomical grounds.

In summary, the distinctive patterns of connectivity of the monkey entorhinal, perirhinal, and parahippocampal cortices raise the possibility that each of these areas may be contributing in unique ways to memory function. The perirhinal and parahippocampal cortices may be important for visual object and visuospatial memory, respectively. The entorhinal cortex may contribute to memory function in yet another way. The strong

projections from the perirhinal, parahippocampal, and other polymodal association cortices to the entorhinal cortex suggest that the latter area may be in a prime position to synthesize convergent polymodal information. It is tempting to speculate that these convergent polymodal projections to the entorhinal cortex may form the basis for the first stage of relational memory processing as described by Eichenbaum et al.

What do animal models of memory model?

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The model proposed by Eichenbaum, Otto & Cohen, by virtue of its directness, represents definite progress in the quest for understanding the role that medial temporal lobe structures play in various laboratory learning tasks used with animal subjects, especially rats. Its major shortcoming lies in the claim that it applies not only to animals but also to humans. We find that claim ill founded.

A large variety of animal models have been described in the literature. There are animal models of toxicity, brain atrophy, leprosy, drug use, dementia, schizophrenia, delirium, and so on. What one does not find are animal models of things such as artistic creativity, mathematical reasoning, or language. Why not?

We can think of at least two plausible reasons. First, these expressions of the human brain are thought to be so unique that trying to learn something about them – for instance their neuroanatomical correlates – by experimenting with rodents, or even nonhuman primates, is difficult if not impossible. Second, the same reason that there are no human models of olfactory discrimination learning in rats, or climbing skills in monkeys: the models do the job too poorly to throw much light on the real thing.

Now, it is, or at least should be, beyond dispute that human memory is both similar to and different from the memory of rats and monkeys. It seems reasonable to assume that the similarities and differences in memory of these species are comparable to similarities and differences between their modes of locomotion, or their physical appearance.

Given that the similarities do exist, it is reasonable to hope that animal models of memory may illuminate those aspects of human memory that do not distinguish the species. Given that differences exist, it is also reasonable to assume that animal models are less useful, and may even turn out to be downright misleading, for the understanding of those features of human memory that are unique to humans.

The question then becomes exactly what aspects of human memory is Eichenbaum et al.'s model supposed to model? Their answer is "declarative memory," which they claim is characterized by the hippocampal system-dependent relational representations. Declarative memory is said to be "involved in our recall of everyday facts and events. Such memories can be brought to *conscious recollection*, are typically subject to verbal *reflection* or other *explicit* forms of *recall*, and can be used flexibly in a variety of situations outside that of the learning experience." (sect. 4, emphasis added). This sounds acceptable for humans, although we find it more reasonable to assume that conscious recollection and explicit recall characterize episodic but not semantic memory (Tulving 1993). The main problem, however, is how to ascribe declarative memory, as described by Eichenbaum et al., to animals. No one knows any method that would allow one to identify "conscious recollection" in nonverbal animals. No one knows yet how to get the animals to "reflect" on their past experiences. Although the distinction between explicit and implicit forms of retrieval is now firmly established in human memory (Roediger & McDermott 1993; Schacter et al. 1993), it has not yet been introduced into work with animals, presumably because no one knows how to operationalize the distinction in an animal experiment. Finally, in human memory the concept of "recall" is clear and sharp, primarily by virtue of its thoroughly studied contrast to another form of expression of propositional knowledge, namely, recognition. But the same distinction in the study of animal memory is fuzzy at best, and some claim it is meaningless. These simple facts suggest that the concept of "human and animal declarative memory," central to Eichenbaum et al.'s theory, is a Procrustean bed. Facts concerning human and animal memory can be fitted into it, but at a cost of considerable suffering.

There are other reasons why we think that higher forms of human memory, such as declarative memory, cannot be meaningfully modelled by animals. Our critique focuses on the anatomical basis on which research on rats (and also to a lesser degree that on monkeys) relies, and on which Eichenbaum et al. base their hypothesis. We question the comparability of the hippocampal formation of rats, "monkeys,"[1] and man. We base our reservations primarily on morphologic (cytoarchitectonic), hodologic, and phylogenetic criteria, assuming that structural inequalities imply behavioral inequalities.

Eichenbaum et al. state that "with regard to the hippocampal formation, each of the subdivisions of this area is well defined and largely comparable in the monkey and rat." They refer to the paper of Rosene and Van Hoesen (1987) in support of their statement. This is puzzling, because Rosene and Van Hoesen (1987) point to "striking differences between hippocampal formation cytoarchitecture of the rat and the monkey or man as well as clear differences between monkey and man" (p. 353). Rosene and Van Hoesen further point out that an underlying theme of their chapter is that the hippocampal formation of both monkey and man is not simply an enlarged version of the hippocampal formation of the rat, but rather "a structure that has undergone a progressive development in primate phylogeny that is reflected in many levels of its morphological organization (cytoarchitectonics, histochemistry, connectivity) and suggests a functional progression as well" (p. 360).

Similar points have been made by other outstanding comparative neuroanatomists of our day (Crosby & Schnitzlein 1982; Stephan 1975). Stephan (1975) devoted a whole section of his *magnum opus* to "specialities of the human hippocampus," and especially emphasized the differential appearance of the fornical system. He pointed out that the fornix projections to the mammillary bodies increase in importance as one moves higher in the phylogenetic hierarchy, and that the septal projections in man differ distinctly from those of other mammals. Furthermore, in humans (and possibly in other higher primates) the fornix contains isocortical fibers, that is, fibers of nonhippocampal origin. Stephan declared that only a minority of the fimbrial fornix fibers originate from Ammon's horn; the majority originate from the parahippocampal cortex. This being the case, the neuroanatomical foundation of Eichenbaum et al.'s two-stage model (temporary storage and parahippocampal region vs. relational processing and hippocampal formation) becomes shaky, at least for nonprimate species.

Two other prominent changes (Stephan 1975) in the hippocampal formation are especially relevant to Eichenbaum et al.'s model: (1) the proportional relations between the entorhinal cortex and field CA1, and (2) the grossly disproportionate enlargement of this field in human beings. Field CA1 receives the main alveolar afferents from the progressive entorhinal cortex. Stephan found that both structures enlarge to almost the same high degree in man compared to other primates.

Thus, even a cursory glance at the comparative neuroanatomy of the medial temporal lobe region reveals that, on the grounds of elementary cytoarchitectonics of CA-subfields alone, the structures discussed by Eichenbaum et al. lack the comparability needed to justify the conclusions about the similarity of function drawn by the authors. Facts concerning the hodological and biochemical diversification compound the difficulty.

The anatomical disparities of the hippocampal regions of rat, monkey, and man reflect ecological and behavioral adaptations and may lead to emphasizing roles in spatial memory processing (Angeli et al. 1993; Jarrard 1993; Murray et al. 1993 Nadel 1991; Wilson & McNaughton 1993), in attention and expectation (Salzmann 1992), or in (verbal) memory processing (Zola-Morgan et al. 1986).

Furthermore, in humans, the processes of encoding and retrieval of episodic memory may be shared between the hemispheres, with the encoding being primarily guided by left prefrontal regions and retrieval by corresponding areas on the right (Tulving et al. 1994). Both the degree and complexity of functional hemispheric asymmetry and phylogenetic expansion of the prefrontal area make it unlikely that comparable sharing mechanisms exist in the brains of nonhuman species. The results of Tulving et al. (1994) provide further grounds for believing that human and nonhuman memory processes differ qualitatively rather than quantitatively. Trying to understand the unique, highly evolved processes of human memory through animal models makes no more sense than trying to understand mathematical reasoning or artistic creativity using the same methods.

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NOTE

1. Although it may be reasonable to speak about "the rat," the general reference to "monkey" is unjustified. Huge differences – in brain development, natural habitat, social behavior, life span, and so on – exist among the hundreds of species ranging from tiny ratlike creatures to nearly human-size species (Stephan et al. 1988).

Hippocampal neuronal activity in rat and primate: Memory and movement

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1. Hippocampus and recognition memory. Recognition memory is usually defined as the encoding of familiarity, an innate ability to determine that a stimulus has been seen previously. Neurons responding on the basis of familiarity are found, albeit rarely, in the brain (Rolls et al. 1982; Wilson & Rolls 1990). Eichenbaum, Otto & Cohen argue that the hippocampus contributes to recognition memory, but their definition is atypical: the encoding of similarity/difference between two highly familiar stimuli; hippocampal neuron firing "reflects only the outcome of the match or non-match judgment" (Otto & Eichenbaum 1992b). These judgments were acquired through training; moreover, they were intimately linked to learned behavioral responses. I speculate that the neuronal firing reflects the learned behavioral contingencies (see below) and are not an expression of recognition memory per se.

Hippocampal neurons encoding stimulus familiarity were not found in studies requiring recognition of words (Heit et al. 1990), serial recognition of objects (Wilson et al. 1990), incidental recognition/matching of patterns (Riches et al. 1991), and continuous recognition/nonmatching of odors (Otto & Eichenbaum 1992b). These findings are consistent with the modest effect that hippocampal/amygdaloid damage has on recognition memory, in contrast to perirhinal damage (reviewed by Eichenbaum et al.) Rolls et al. (1993), however, have found hippocampal neurons that respond to novel stimuli.

2. Hippocampus and sensory information. Eichenbaum et al. argue that "the hippocampal formation does not store specific sensory information," and their cue-sampling cells did not show striking specificity for particular odors (Otto & Eichenbaum 1992b). Our collective data are in agreement. First, hippocampal neurons are not especially responsive to visual stimuli outside the contingencies of behavioral tasks. Second, responses to visual stimuli within a task are modest, often with variable and long latencies (relative to temporal cortex). Third, "visual" responses are often related to the learned contingencies/responses of the task. There are two concerns, however. First, in view of the longitudinal organization of the hippocampus (Amaral & Witter 1989; Friedman & Goldman-Rakic 1988; Riches et al. 1991; Watanabe & Niki 1985; Wilson et al. 1990), it will be necessary to show that visual and olfactory information is carried to the site of "unresponsive" neurons. Second, it is possible that weak neuronal responses do not accurately reflect function. Hippocampal neurons could be extremely stimulus-selective and thus rarely activated.

3. Hippocampus and movement. Although stimulus novelty/familiarity did not influence hippocampal responses in our experiments, hippocampal activity was clearly related to the behavioral responses. The matching task required the monkey to select a spatially directed movement on the basis of nonspatial (object/pattern) stimulus information (presented centrally on a video monitor). A range of sensory-motor types was found (see also Heit et al. 1990; Otto & Eichenbaum 1992b: Ranck 1973), including those selective for specific directional movements. Upon examining neuronal activity in relation to the time of the completed arm movement, it was apparent that hippocampal activity frequently predicted the intended goal/location of the hand as it moved to the target. This is reminiscent of place cell activity (Muller & Kubie 1989), head directionality (Taube et al. 1990), and observations of hippocampal activity related to eye (Ringo et al. 1994) and whole-body movement (O'Mara et al. 1994).

Movement-related hippocampal neuronal activity was also observed by Otto and Eichenbaum (1992b): "peak firing is best time-locked to behavioral acts central to odor cue acquisition and to the match/non-match decision." Although a variety of cell types were found, they could be attributed to head movements into and out of the sniff port, maintaining head position, head movements upwards to water port, and so on. However, Figure 4 (Otto & Eichenbaum 1992b) clearly shows dissociations between neuronal activity and movement.

4. Hippocampus and declarative/episodic recall. Eichenbaum et al. argue that the hippocampus is important when "retention depends on representation of relations among cues . . . or on specific episodes with familiar stimuli." As an illustration, they refer to the match/nonmatch responses of hippocampal neurons (Fig. 4, Otto & Eichenbaum 1992b). Although Eichenbaum et al. emphasize hippocampal encoding of relationships between sensory events, their hippocampal neurons seem most responsive when movements are going to be made, and we have found that hippocampal neurons are most responsive to visual cues when those cues require a behavioral response.

Is it possible to reconcile movement-related hippocampal activity and Eichenbaum et al.'s hypothesis? As a step in this direction, I suggest that declarative memory is exemplified by the recall of information for previous actions and their outcomes

(or actions in relation to sensory events) and is manifested in hippocampal movement-related activity. Preliminary data obtained during a delayed alternation task showed that hippocampal neurons responded in this task and reflected access to memory for previous actions (Wilson et al. 1990). This movement-related activity could reflect relational encoding, or its utilization for the selection of behavioral responses in tasks requiring episodic memories without explicit sensory cues to guide behavior (e.g., radial arm maze, differential reinforcement for low response rate and delayed alteration).

Eichenbaum et al.'s hypothesis accounts for much behavioral data. The next step will be to specify mechanisms by which the hippocampus modulates memory, or behavioral actions guided by memory.

Authors' Response

The hippocampal memory system and its functional comments: Further explication and clarification

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The comments, questions, and criticisms raised in the commentaries covered a great deal of territory, much of it divisible into the following two major areas: (1) There were concerns with the nature of our enterprise, including our rationale (a) for trying to develop an animal model of human memory and thereby bring the animal model literature into correspondence with the human amnesia literature and (b) for trying to identify and characterize the brain's multiple memory systems and their component "functional units." (2) There were more specific concerns with the particular characterization we offer of the functional role of the hippocampal system in memory and the distinct functions of the hippocampal formation and parahippocampal region. In responding here to what seem to us the more serious questions and concerns raised, we attempt to clarify our general approach and to further explicate and elaborate the specific functional characterizations proposed, addressing particular issues highlighted by different commentators as outline in Table R1. We have elsewhere provided a much more extensive explication of our approach and of our theory of hippocampal system functioning (Cohen & Eichenbaum 1993), and do not have the space here to make all the points and marshall all the arguments we used there. Accordingly, in some instances we must refer readers to that more thorough presentation of our theoretical position. However, as the target article was intended to go beyond our earlier proposals by identifying and characterizing the role of two component functional units of the hippocampal system, we take the opportunity here to further clarify several critical aspects of our position.

R1. On attempting to develop an animal model of human memory and to bring the animal model literature into correspondence with the human amnesia literature regarding the role of the hippocampal system in memory

Our goal has been to articulate the functional role of the hippocampal system in memory so as to allow us to make experimental predictions for studies on any species and to make contact with work about both cognitive processes and neural mechanisms. We believe a convergence of findings and of ideas from cognitive science and neurosciences provides the critical clues and constraints for developing a more comprehensive cognitive neuroscientific understanding of memory. The theory of the hippocampal memory system described in the target article (and in more detail in Cohen & Eichenbaum 1993) accounts for all of the following: (1) the pattern of spared and impaired memory performances in both amnesic patients and animals with hippocampal system damage, (2) the activity of neurons in the hippocampal system in behaving animals during memory performance, and (3) anatomical facts concerning the hippocampal system. Only if we are right in attributing to the hippocampal system a functional role that is conserved or comparable across species, and only if we are right that one can tie behavioral, physiological, and anatomical facts to the underlying representational properties of the hippocampal memory system, will it be possible for our enterprise to succeed. To the extent that our account manages to handle these different domains of data, our assumptions will have been validated.

In the face of the unresolvable incompatibility between **Tulving & Markowitsch**'s assertion, on the one hand, that efforts to understand the nature of declarative memory must be concerned exclusively with memory studies in humans (because declarative memory is not present, or cannot be assessed, in animals), and **Solomon & Yang**'s suggestion, on the other hand, that the study of a single, simple memory phenomenon (eyeblink conditioning, primarily in rabbits) provides an adequate domain of inquiry for understanding hippocampal function, we suspect that our strategy of bringing together in our proposal various domains of memory research is the more productive one. In contrast to **Grossberg**, we do believe it is useful to focus on *real* rather than ARTificial neural systems. Computational models will certainly be helpful in understanding how functions are accomplished by components of the hippocampal system, but we first need to identify and characterize the function of those components. The fact that the remainder of the commentators do address specific comments to our hypothesis perhaps puts these criticisms about the proper domain of useful discourse into a broader context.

There are two further points to be made here. First, in addition to anatomical data cited in the target article, new findings from Amaral and colleagues (Amaral & Leonard 1993; Burwell & Amaral 1993) provide compelling evidence of fundamental similarities in the cortical-parahippocampal and intrinsic hippocampal circuits in rats and primates. Rather than reflecting circuitry differences in the hippocampal system itself, what cross-species differences do exist may be largely a consequence of the dramatic evolution of human cortical areas that feed into and receive feedback from the hippocampal system.

Table R1. *Organization of the authors' response to specific commentaries*

Topics	Commentators
R1. On attempting to develop an animal model of human memory	Grossberg, Solomon & Yang, Tulving & Markowitsch
R1.1. Identifying the hippocampal "memory system" and its component "functional units"	Bolhuis & Reid, Grossberg, Horel, Katz & Steinmetz, Mayes, Shapiro
R1.2. Why it's possible and useful to designate functional units	Aggleton, Brown, Fuster, Good & Morris, Hampson & Deadwyler, Jarrard, Miller, Rawlins et al., Squire et al., Suzuki
R1.3. "The hippocampal system" and "the declarative memory system"	Aggleton, Good & Morris, Mayes
R2. Elaborating and updating our proposals about the roles of the hippocampal formation and parahippocampal region	
R2.1. Testing predictions of this (or any) theory of hippocampal function	Aggleton, Bingman, Bolhuis & Reid, Gray et al., Good & Morris, Humphreys & Dennis, Mayes, Nadel, Rapp, Rawlins et al., Shapiro
R2.2. The domain of hippocampal function	Grossberg
R2.3. Relational memory, associations, and conditioning	Bolhuis & Reid, Good & Morris, Katz & Steinmetz, Nadel, Solomon & Yang
R2.4. The hippocampus and behavioral output	Gray, Wilson
R2.5. The temporal domain of hippocampal function	Fuster, Hampson & Deadwyler, Kesner
R2.6. Is spatial special?	Bingman, Nadel
R2.7. An updating of our conception of the role of the parahippocampal region	Brown, Gluck et al., Horel, Jarrard, Murray
R2.8. Distinguishing cue compression from relational representation: the danger of confusion	Fuster, Gluck et al., Good & Morris, Jarrard, McNaughton, Murray

Thus, we suspect that **Tulving & Markowitsch** are wrong in relying on the gross morphological and cytoarchitectural data that suggested important species differences to some of the outstanding anatomists of an earlier day (circa 1975); instead, we defer to the findings from modern anatomical tracing methods indicating conservation of the fundamental circuitry and cortical connections across species.

Second, with regard to **Tulving & Markowitsch**'s objection to exploring declarative memory in animals, the proposal we offer concerning its nature and representational characteristics specifically bridges human and animal memory. We argue that the relationality and representational flexibility of declarative memory allows it to be accessed by various brain processors and expressed in various (even completely novel) contexts. Among the many processors to which declarative memories are accessible are those supporting humans' ability to consciously recollect their experiences and to provide cognitive mediation of (certain) behavior. Our theory is *not* about how cognitive mediation and conscious recollection are instantiated in the frontal lobe and related brain systems; that would need to rely on the study of humans. Rather, our theory holds that such declarative memory provides the data base on which such processors, and many others, operate – in both humans and animals. The fact that rodents and primates with hippocampal damage are so systematically and profoundly impaired on tasks requiring relationality and representational flexibility suggests that we have succeeded in offering a characterization of declarative memory that can indeed extend to the study of animals, a feat that no other theory derived from the study of human memory has accomplished.

R1.1. Why seek to identify and characterize a hippocampal "memory system" and its component "functional units"? Our theory, in agreement with many other views of hippocampal function, holds that the hippocampus and closely related structures serve memory by assisting the neocortex in its job of long-term memory storage. In our view, the hippocampal system does this job by helping to mediate the binding together of perceptually distinct objects – via converging inputs from and diverging outputs to the various cortical processors – in order to create flexible, relational representations of the events and scenes we experience. We attribute to the hippocampal system a particular set of memory processes in the service of a particular kind of memory.

Contrary to **Horel**'s suggestion, we do not seek to isolate memory to the hippocampus, or to gerrymander the anatomical identity of the hippocampus to accomplish this. Thus, as outlined in Figure 1 of the target article, we view memory as being mediated by a large set of interacting structures, including many neocortical association areas as well as the several anatomically distinct subdivisions of the hippocampal system. A useful simplification of our framework is to view the hippocampal system as two stages of cortical processing that follow those performed within the unimodal cortical processing systems. Thus, for example, visual information processing is accomplished through a long series of cortical "modules" that combine elemental features of visual perception,

ultimately reaching the last stage of unimodal processing in the inferotemporal area where whole visual objects may be identified (e.g., Tanaka 1993; Van Essen et al. 1990). The next stage of cortical processing is seen as the parahippocampal region, where a convergence and extended storage of multimodal information occurs. Finally, the outputs of the parahippocampal region are processed by the hippocampal formation where relations among items are detected and arranged. Horel did not seem to be horrified by the "trucking" of visual information across broad cortical expanses involving tens of visual processing stages to accomplish visual recognition; he balked only at the notion that adding just two more stages of hippocampal processing could mediate the combining of several such streams of unimodal information for the purpose of relating visually recognized objects to other items in memory.

Is something special happening in the hippocampal system, other than the combining of unimodal channels of information? Yes. Is this system just a "tape recorder" of multimodal memories? No. We see cortico-hippocampal interactions as extensions of the kinds of bidirectional interactions attributed to cortico-cortical connections in unimodal sensory processing systems. Thus, for example, Damasio (1989) has suggested that combinations of forward and backward projecting connections within visual and other sensory systems might subserve first a forward processing hierarchy that assembles a perceptual object and then backward processing that recovers object details from the general concept of an object. Our proposal extends this notion; we see the forward projections through the hippocampal system as supramodal convergence and the backward-projections from the hippocampal formation to the parahippocampal region, and those from the parahippocampal region to neocortical areas, as critical to the organization of cortical storage and perhaps also retrieval, at least for some period of time[1] (Squire et al. 1984). Consistent with **Horel**'s argument that processing and memory are intertwined in all brain structures, but contrary to **Grossberg**'s preference for no memory storage in the hippocampal system, our view is that each component of the declarative memory system performs a specific kind of "processing" and each area is plastic in that its subsequent processing is influenced by previous experience. What makes structures of the medial temporal lobe "special" to memory is that they communicate bidirectionally with all of the higher-order unimodal and multimodal cortical processors and that the organizing process the hippocampal system performs contributes to the nature of memory storage for all information modalities. In this way the hippocampal system plays a "global" role in memory formation.

R1.2. Why it's possible and useful to designate functional units of the hippocampal system. Our identification of functional units in the hippocampal system is intended to disentangle the complicated behavioral effects of lesions in different components of the system and to help us understand the differences in neuronal firing patterns in these areas. It is implicit in the design of our model that we are *not* attempting to localize memory within the hippocampal system or to compartmentalize memory functions into independent "black box" anatomical structures. Rather, we recognize and emphasize that memory formation involves the interactions between the cortex and hippocampal system, and further, that processing in the hippocampal system involves interactions among its distinct subdivisions. The central question is: *which* hippocampal areas compose functional "units" and *what* are the distinct processing contributions of those units? When we claim that intermediate-term storage of individual representations is "orthogonal" to relational representation, we mean that these functions can be *dissociated* experimentally and *associated* with particular components of the system.

To facilitate this effort we try to combine cytoarchitecturally distinguishable subdivisions of the medial temporal area into functionally cohesive units. We think this is appropriate because some of the subdivisions of the hippocampal system are so closely linked that they probably act together to mediate particular processing functions and those functions might be different for those of other groups of subdivisions. Our approach in designating the functional units is not arbitrary, as **Jarrard** and **Good & Morris** suggest – it is based on the modern analyses of circuitry and neuropsychological evidence offered in section 1.2. Based on anatomical and physiological considerations, Shepherd (1974) concluded that the components of the trisynaptic circuit operate together as a processing "module," just as layers of neocortex operate in cortical modules. Our updating of this circuit to include the subiculum is based directly on more recent anatomical observations indicating that this area is very much a part of the serial and parallel design of the intrinsic hippocampal circuit (Amaral & Witter 1989; see target article sect. 1.2). **Suzuki** goes further to suggest that the entorhinal area might be better assigned as yet another component of the intrinsic hippocampal circuit. We stopped short of this based on Witter's characterization of the parahippocampal region as involving close interactions among the laminated cortical areas surrounding the hippocampus. Whether Suzuki's or Witter's view of the operational units is more correct cannot be decided solely from circuitry considerations, but it is gratifying to see the level of scholarship raised above that of the historical nomenclature Jarrard and Good & Morris prefer.

Even though our initial groupings of cytoarchitectural subdivisions were inspired by circuitry considerations, the question of whether they act together as a "functional unit" requires a clearcut behavioral assessment. Our assessment was based on the following set of operational principles in defining a functional unit: (1) A complete lesion of a functional unit produces the maximal effect that can be observed with any lesion of the entire system of units. (2) Subtotal lesions sparing the functioning of parts of a functional unit produce only partial behavioral effects. (3) Conversely, larger lesions exceeding the functional unit produce no greater effect on the behavioral function than a lesion restricted to the unit. Applying these principles requires a careful consideration of the parallel and serial connectivity of subdivisions in a functional unit and the effects of different lesions on these connections as well as on the structural areas. Only lesions of a subdivision that spare the input and output connections of other subdivisions, as well as their cells, are expected to result in partial deficits. Thus, for example, a neurotoxic ablation of the subiculum that spares direct connections between the parahippocampal region

and the dentate gyrus and Ammon's horn is expected to produce a partial behavioral deficit. Conversely, lesions that are restricted to the locus of a subdivision but incidentally disconnect other elements are expected to have the combined effects of lesions of all the subdivisions. Thus, a radiofrequency lesion of the subiculum, a transection of the fornix, or an ablation of the parahippocampal region that completely disconnects the subcortical or cortical connections of all subdivisions of the hippocampal formation are expected to have the effect of a complete hippocampal formation ablation.

How do these principles fare in their application to our designations of functional units in the hippocampal system? With regard to the hippocampal formation, **Jarrard** has argued that the appropriate functional unit is restricted to the "hippocampus," which in his terminology refers to Ammon's horn plus the dentate gyrus. However, data from his own elegant experiments using selective neurotoxic lesions of subdivisions of the hippocampal formation indicate that the subiculum should be combined with Ammon's horn and the dentate gyrus as a functional unit. To make this point we have replotted the data from his experiment comparing the effects of selective and combined lesions on both spatial and nonspatial radial arm maze performance (Fig. R1; Jarrard 1986). On spatial reference memory (learning to avoid consistently unbaited maze arms), lesions of Jarrard's "hippocampus" (hippocampus plus dentate gyrus) and those of the subiculum each produce partial deficits compared to the effects of combined ablation of both structures. On the working memory variant of the task (learning to visit baited arms once, see sect. 4.4) guided by either spatial or nonspatial cues, the same comparison is even more striking. Lesions restricted to the hippocampus or subiculum each result in minimal impairments, but the combination

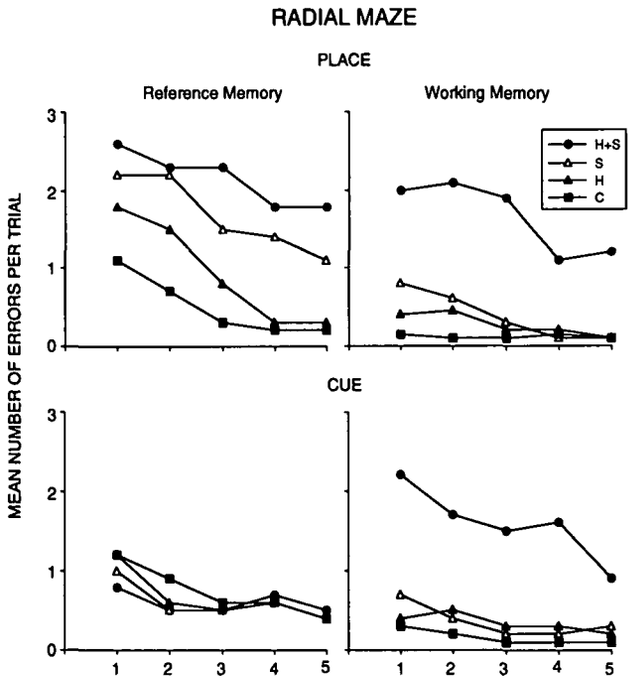

Figure R1. Performance of normal control rats (C) and rats with selective neurotoxic ablations of the "hippocampus" (H; hippocampus plus dentate gyrus), subiculum (S), or the entire hippocampal formation (H + S) on working and reference memory in the radial arm maze task. Taken from Jarrard 1986.

lesion including all elements of the hippocampal formation produces a severe impairment, as large as the deficit in spatial reference memory. Precisely the same findings, indicating that a severe and persistent deficit only follows complete ablation of the hippocampal formation, were reported in Jarrard's collaborative study with Morris using the water maze (Morris et al. 1990). Thus, selective neurotoxic lesions of the hippocampus or subiculum produce partial and equivalent effects compared to that of the combination lesion (ablation of the entire hippocampal formation) in various forms of spatial learning. The impact of sticking to the old, if conventional, designation of the hippocampus as including only the elements of the trisynaptic circuit is profound. Not only is one left with two structures (subiculum and hippocampus) that seem to have the identical function, but one fails to detect the full domain of the functions subserved by the whole functional unit. In the case of the radial arm maze, once the analysis of separate and combined lesions reveals that the functional unit for spatial performance is the entire hippocampal formation (Fig. R1, top panels), the functional domain can be seen to include both spatial and nonspatial working memory (Fig. R1, right panels). Finally, considering the principle that lesions larger than a functional unit are expected to produce no larger deficit, Jarrard has also found that an ablation of the entorhinal area that appears to include perirhinal cortex (see Jarrard et al. 1984), a lesion that disconnects all hippocampal areas and removes nearly the entire parahippocampal region, produces radial arm maze deficits similar in pattern and magnitude to those of complete ablation of the hippocampal formation. In the same study he also showed that transection of the fornix, which disconnects all parts of the hippocampal formation from subcortical areas, produces the same pattern and magnitude of impairments.

A parallel analysis of the parahippocampal region supports our contention that subdivisions of this cytoarchitecturally heterogeneous area may act as a functional unit (Fig. R2). In a recent study on the cortical contributions to performance on delayed nonmatch to sample, Meunier et al. (1993) showed that lesions of perirhinal cortex or those of the entorhinal area each produced significant impairment, but each separate lesion produced less effect than the combined removal of both areas (called by them the "rhinal cortex"). Notably, lesions that remove the rhinal cortex plus hippocampal formation produce a deficit that is similar in pattern and magnitude to ablation of the entire hippocampal formation plus rhinal cortex. It is important to note that these lesions included minimal damage to the third subdivision of the parahippocampal region identifiable in monkeys, specifically the parahippocampal gyrus (areas TH and TF, see sect. 1.2). It is quite possible, as suggested by these behavioral results, physiological data by **Brown,** and on anatomical grounds by **Suzuki,** that the parahippocampal gyrus may not play a critical role in intermediate-term storage for visual object representations but may be included for information in other modalities. It may well turn out that there exist specificities according to *sensory modality* based on differential connectivities at the input side of the hippocampal system, but at this point we see no evidence to suggest that the *memory processing* functions of subdivisions in the parahippocampal region differ. Finally, **Rawlins** and his colleague (Yee & Rawlins, in

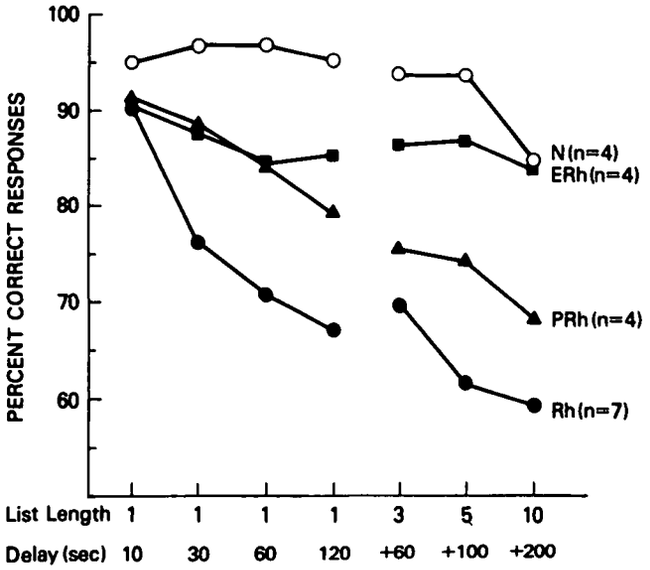

Figure R2. Performance of normal monkeys (N) and monkeys with selective aspiration ablations of the entorhinal cortex (ERh), perirhinal cortex (PRh) or the combination of these lesions (called rhinal cortex; Rh) on object-cued delayed nonmatch-to-sample with different delays (left) and different length "lists" of objects to remember. Taken from Meunier et al. 1993.

preparation) report that the fact that neurotoxic lesions of the entorhinal area do not block object recognition may be attributable to the failure to include the perirhinal area in his lesion.

The concept of "functional units" suggests a number of experiments that could address specific predictions generated by our model. For example, as noted by **Squire et al.**, one strong prediction is that a complete removal of the parahippocampal region should not exacerbate the deficit on a relational learning task (e.g., spatial working memory) resulting from complete destruction of the hippocampal formation. Combined parahippocampal-hippocampal lesions have not yet been tested on this type of task, and they should be, but it seems likely that perirhinal-entorhinal lesions that completely interrupt cortical-hippocampal connections may well be an adequate substitute; as noted above, Jarrard (1986) has shown these lesions to be no more effective than complete hippocampal formation lesions. In addition, those (e.g., **Aggleton**) who would seek to test this aspect of our hypothesis must keep in mind the expectation that partial lesions of the parahippocampal region that spare cortico-hippocampal connections are not expected to eliminate hippocampal processing.

Finally, considering complementary evidence from unit recording studies, **Brown, Fuster, Hampson & Deadwyler,** and **Miller** have argued that one does not observe absolute functional distinctions between the neocortex, parahippocampal areas, and hippocampus. They have noted that some proportion of cell types observed in any of these areas is observed in them all. Yet, in agreement with our general conclusions, Brown, Fuster, and Hampson & Deadwyler concur about the functional distinctions proposed, based on differences in the *proportions* of cell types observed in different areas. This point may be well taken, although it does not cause us to alter our interpretation of that data. A decisive analysis of this issue awaits a complete exploration of several neocortical areas as well as the entire parahippocampal region and hippocampal formation using the same recognition memory task.

Miller raised stronger objections to our conclusions, although the relevance of his contentions are limited in two ways: (1) his comments were restricted to distinctions between the firing patterns of the neocortex and the parahippocampal region and did not consider the hippocampal formation; (2) he also restricted his considerations to data derived from his experiments on working memory rather than on recognition memory, which was the focus of our considerations (for a review of the distinction between these types of memory see sect. 4.4). In addition, he departed from his previous conclusions based on consideration of a broader data set (see Miller et al. 1993, p. 1474, and sect. 5.2). Miller's point that cells in neocortical areas can acquire persistent learned responses with repeated experience requires us to remind the reader of a central premise in our model; cortical areas are the locus of permanent memory storage (Fig. 1). There should be no surprise to see long-term storage phenomena in the cortex eventually – the question is when? To examine this question, we gave greater weight to data from recognition memory experiments in which new items were presented briefly, establishing only transient memory representations. Only with this paradigm can one then examine and compare the persistence of neural correlates of memory in different areas. Based on this criterion, none of Miller's data are fully relevant because his animals were given considerable experience with the test stimuli prior to and during the course of recording. The "active memory" neural correlates observed in prefrontal cortex, V4, and a poorly defined area including inferotemporal and perirhinal cortex, reflected the working memory demand for judgments about the relative recency of frequently recurring stimuli. By contrast, our summary emphasized the transient representations that occur after brief initial presentations to single novel stimuli, and the findings were consistent with our model attributing to the parahippocampal region memory representations with greater persistence and less susceptibility to interference than those in the neocortex. Nevertheless, as we had pointed out in the target article, our review was based on incomplete data with regard to the full survey suggested above.

R1.3. "The hippocampal system" and "the declarative memory system." It has been noted by both **Aggleton** and **Mayes** that there are no diencephalic regions in our hippocampal "memory system." These were excluded fully recognizing that damage to the medial thalamus produces some deficits in memory performance similar to those of hippocampal lesions, simply because there are also a number of studies indicating unique aspects in the pattern of deficits following damage to these areas (this issue is reviewed in Cohen & Eichenbaum 1993). Aggleton's mention of the connection between the fornix outputs of the hippocampal system and diencephalon is quite appropriate, and serves to highlight the eventually artificial hippocampal system boundary we draw at the fornix itself. Furthermore, contrary to how **Good & Morris** wish we would present it, the hippocampal system is not equivalent to the declarative memory system – we quite agree with Aggleton and Mayes that the full

declarative memory system includes more components, such as the neocortical storage sites, as we noted above, and the midline diencephalic structures. When there is further work on the latter brain area, in which physiological, anatomical, and behavioral data are brought together as for the hippocampal system, there will be more to say about how the functional roles of these different regions compare and contrast. The bottom line is that there are relatively few animal studies comparing the memory effects of medial thalamic and hippocampal damage. In particular, virtually no animal studies have examined the deficit in memory representation following these lesions; we have suggested that this would be critical (see target sect. 4.1).

R2. Elaborating and updating our proposals about the roles of the hippocampal formation and parahippocampal region

Assuming for the moment that it is useful to designate functional units within the hippocampal memory system, we will now reconsider how we characterized the functional contributions of those areas, further defending the specific conclusions we arrived at.

R2.1. Testing predictions of this (or any) theory of hippocampal function. Several commentators questioned the "testability" of our hypotheses regarding the specific functional assignments of the hippocampal formation and parahippocampal region, making the point that one must be able to predict proactively, that is, before the experiment is carried out, the pattern of performance deficits in animals with damage to these systems rather than offering explanations of the results after the fact (**Aggleton, Bingman, Bolhuis & Reid, Good & Morris, Gray et al., Humphreys & Dennis, Nadel, Rapp, Rawlins et al., Shapiro**). There is no question about that. We all (well, most of us, anyway) have predictions in mind when we design experiments. But how explicit and how public are those predictions? How precisely do they specify an expected outcome? It is important to know at what level of analysis the predictions are formulated. In our more extended presentation (Cohen & Eichenbaum 1993), we devote a chapter to the question of how to test our theory of the (whole) hippocampal system's functional role in memory.

Whereas **Nadel** bemoans the absence of "a world of clean data, perfectly placed lesions, and well-specified theories," we believe that the problem in interpreting the vast set of behavioral results of hippocampal system damage and in predicting new ones has to do with predictions (and theories) being posed at the wrong level of analysis. There is a misdirected emphasis on performance predictions. In our view (outlined in sect. 4 and more thoroughly in Cohen & Eichenbaum 1993), virtually any task can be accomplished by either hippocampal system-dependent or hippocampal system-independent representational strategies. This means that one cannot predict definitively for any particular task with a particular set of variable settings that hippocampal damage will result in impairment, no effect, or even facilitation. As noted by **Rawlins et al.**, it turns out that there are lots of examples of seemingly idiosyncratic parameter manipulations that give us results not specifically predicted by any theory. This is, unfortunately, the case, *unless* we have further information about the behavioral strategies – and the representational demands of those strategies – used by the subjects on that task. Thus, while **Humphreys & Dennis** emphasize the use of formal descriptions of tasks, it is growing ever clearer that tasks with identical formal descriptions (e.g., nonspatial working memory; simultaneous or successive odor discrimination learning [see **Bolhuis & Reid**]; recognition memory; conditional discriminations) are often accomplished in different ways by subjects, depending on the variables over which we exert little control.

Some have proposed that the appropriate strategy for this problem is to depend upon tabulating the experimental results and determining the "winning" theory by election, as it were, producing just the mixture of results apparent in the tabulations of **Gray** (Gray & McNaughton 1983) and **Nadel** (O'Keefe & Nadel 1978). But this just reifies the importance of those as yet unidentified and poorly appreciated controlling variables without providing a way to understand how they alter the representational demands of the task. For example, the number and constancy of visual objects in the nearby environment of animals performing, say, a radial arm maze or water maze task may well influence whether the animal tries to learn (and depend upon) the compositional relationship among the objects rather than "compressing" the representations of the items (see the sections on cue compression below); we would predict impairment following hippocampal system damage if and only if the animals use the former strategy. Likewise, in "repetition priming" tasks in humans, we have come to appreciate that the number of items presented in an initial study phase will determine how much explicit remembering (declarative memory) of the list items will effect subsequent priming performance and hence whether or not amnesic patients will show performance comparable to that of control subjects (see **Mayes**).

A far more valuable strategy, we argue, is to close the gap between theories of memory representation and measures of behavioral performance by attempting to understand the underlying memory representations subjects use to solve a particular type of learning problem. As we have suggested here and elsewhere (Cohen & Eichenbaum 1993; Eichenbaum et al. 1992a; 1992b), this can be accomplished by presenting experimental subjects with a range of very similar tasks that vary the demands on a particular type of memory representation, and then *predicting* the pattern of performance differences between intact and brain-damaged subjects in accordance with variations in the nature of the representational demand. Moreover, an even more critical strategy is to apply behavioral probes, transfer tests, or control experiments that determine the nature of successfully acquired memory representations by examining how subjects use what they have learned. We *predict* that the (only) memory representations of a given new-learning situation that would be available to subjects with hippocampal system damage are of the inflexible, individual kind we attribute to procedural memory. It is based on this criterion, rather than on "pick your own" as **Gray et al.** have suggested, that we have emphasized experiments that have used probe tests such as those of Eichenbaum et al. (1989;

1990) and Saunders and Weiskrantz (1989). We note **Rapp**'s endorsement of this strategy. The strategy based on using the electoral process described above – what we refer to as psychoarithmetic – is just not adequate.

Of course, for the many studies of the effects of hippocampal system damage that have already been conducted without using either the strategy of probe testing or the strategy of systematically varying the nature of the representational demands we advocate, we must resort to *post hoc* explanations, conjectures really, about results from isolated experiments, just as does anyone else who would test the robustness of a particular theory. But we believe we have a rational, theory-based way to proceed. That is not to say it is easy. For example, take **Nadel**'s reminder about the performance of monkeys with hippocampal lesions on transposition, a paradigm intended to test for "relational" learning. He got the results wrong – those monkeys actually performed better than normal animals (facilitation rather than no impairment) early in the transposition phase, which provides a more valid test of transfer. However, this finding can readily be explained when one looks closely at the fact that the investigators began with reversal learning to reduce the monkeys' performance below "ceiling" level on pattern discriminations. Unfortunately, the transposition test involves yet another semi-reversal (reversing the reward value of one of the stimuli). It is accordingly most likely that the facilitation is attributable to the fact that monkeys and rats with hippocampal damage learn easy reversals more rapidly than intact animals (Eichenbaum et al. 1986a, Zola & Mahut 1974); it probably has nothing to do with transposition, which could not be tested directly with this paradigm, regardless of what the investigators had intended.

Finally, **Nadel**'s warning about the danger of circularity is quite appropriate for all theories. He might have remembered to apply it when claiming that "damage to the hippocampus *always* causes learning deficits in a certain well-defined kind of spatial task that we have called 'place' learning." Which spatial tasks exactly? It turns out to be just those on which subjects with hippocampal damage are impaired. To offer but one example of the circularity in the spatial mapping theory, rats with hippocampal lesions are impaired in delayed alternation but not left-right discrimination guided by the same spatial cues. Why? O'Keefe and Nadel (1978) have argued that only the former is a true "place" task, even though all the available spatial and other cues are identical in the two tasks. They explain that a simple "turning" or orientation strategy is sufficient to solve the left-right discrimination. Why can't the rats with hippocampal damage learn to alternate "turns"? It seems they just do (e.g., in most operant boxes) or don't (e.g., in most mazes), depending on subtle task parameters, but this could not have been predicted in advance. Similar *ad hoc* explanations for many other results haunt the spatial mapping theory and all theories of hippocampal function. We need to change the way we go about testing theories and, in doing so, we must develop behavioral assessments aimed at a level of memory representation that can account for all the data.

R2.2. The domain of hippocampal function: Why a general role in "relational representation"? In our view, too many accounts of hippocampal function have focused on limited domains of analysis. For example, proponents of the "configural association" theory (see target article sect. 4.5) focus on whether or not impairment will be observed on a limited set of compound-cue learning tasks, failing to seriously address the much larger problem of how such a theory could account for performance in tasks like differential reinforcement for low response rate (DRL), spatial learning, working memory, and others. It is in the effort to avoid a "limited domain" account of hippocampal function that we have presented such a broad view of the function of the hippocampal formation (see Cohen & Eichenbaum 1993, for a full treatment). Nevertheless, we elaborate a particular definition and strict boundaries for the domain of relational representation below. The concept is not, as several commentators have suggested, the same as association. If it were, the theory would mean no more than memory itself, yet a central claim is that the role of the hippocampus is restricted to a particular form of memory representation. Also, it is not that we believe the hippocampal system is involved in many *functions*, as **Grossberg** claims; rather, we argue that the relational processing attributed to this system contributes to performance in many behavioral *tasks*.

R2.3. Relational memory, associations, and conditioning. Let us begin by exempting stimulus-reward and stimulus-response "relationships" in conditioning from what we mean by relational representation (see commentaries by **Bolhuis & Reid, Good & Morris, Katz & Steinmetz, Nadel, Solomon & Yang**). To understand the distinctions between conditioning and relational representation, it helps to consider what is learned and what learning is assessed during examples of seemingly "simple" associative conditioning in humans and animals. When humans learn that a certain food wrapper contains a pleasant tasting candy, we learn about the wrapper, about the taste of the candy, and about the relationship between these two arbitrary stimuli. We also become attracted to the wrapper when we see it again, because we felt good during the previous experience. Thus, two forms (at least) of learning were going on during the initial experience: (a) a relational representation involving the "arbitrary" stimuli that characterized the wrapper and the taste of the food, and (b) the acquisition of familiarity for and the adoption of a positive bias towards the wrapper. One can test human subjects for both types of learning somewhat directly. Knowledge about the relationship between a food and its wrapper is revealed through declarative memory expression during inquiry about what is in the wrapper; this is the kind of memory impaired in amnesia. By contrast, pure familiarity and biasing phenomena like the latter can be unconscious, revealed through implicit changes in behavior associated with the stimulus, and spared in amnesia (see Cohen & Eichenbaum 1993, for other examples of impairment of explicit knowledge and sparing of implicit performance with the same material in amnesia).

In conditioning experiments where animals are trained to associate a particular CS with a reward, the subject may well be learning both a relationship between arbitrary cues, for example the appearance of the CS and the US, and the adoption of a bias towards the CS. However, since typical assessments of performance only require that the animal approach the CS, learning requires, and probably reflects, only the acquired positive bias towards the CS or the adoption of a particular response in its presence.

Thus, conditioning performance does not provide a clear test of whether the animal has learned anything about the relationship between the visual stimulus and the gustatory or other sensory qualities of the food reinforcer. In other terms, our notion of relational representation is restricted to the organization of relations among *arbitrary* stimuli and, by definition, reinforcers are *not* arbitrary stimuli – they bias responses toward arbitrary stimuli with which they are associated. Furthermore, our exclusion of this type of learning from the domain of hippocampal processing is certainly not new. Others have referred to the hippocampal system-independent acquisition of stimulus-reward and stimulus-response associations as "dispositions" for individual stimuli (Thomas & Gash 1988), the acquisition of "taxon" strategies involving the orientation toward reinforcing stimuli (O'Keefe & Nadel 1978), or the development of "habits" associated with individual cues (Hirsh 1974).

R2.4. The hippocampus and behavioral output. Other commentators felt we had not adequately eliminated the possibility that the hippocampus may be involved in behavioral output. Thus, **Gray et al.** felt that the hypothesis that the hippocampus is involved in behavioral inhibition has been forgotten but not rejected. Yet several experiments, including our own (Eichenbaum et al. 1986a; 1988), have shown that animals with hippocampal lesions can have normal, facilitated, or impaired learning in paradigms that involve identical requirements for behavioral inhibition. **Wilson** used electrophysiological evidence to reach just the opposite conclusion as Gray did, that the hippocampus is involved in the initiation of behavioral responses. We too have observed that most hippocampal cells fire closely time-locked to behavioral actions, but we have also observed that whether and how much a hippocampal cell fires at that time is critically dependent on combinations or relations among stimuli driving the behavioral response (Eichenbaum & Otto 1993). Our own interpretation of the points raised by Gray et al. and Wilson is that the hippocampus is squarely in the "middle" of the sensory-motor loops of the brain. Because of its anatomical position, neural activity patterns and symptoms of dysfunction in the hippocampus are likely to be associated with both sensory and behavioral variables in particular situations. Nevertheless, one should not be misled by such simple correlations. They are the sort of thing that can most readily be dissociated from the more "central" functions of the hippocampus in cognitive representation and decision making leading to action.

R2.5. The temporal domain of hippocampal function. Several commentators (**Hampson & Deadwyler, Kesner, Fuster**) raised questions about the role of the hippocampal formation itself in "temporal" processing, suggesting that we had incorrectly taken this kind of processing out of the hippocampus and put it in the parahippocampal region. Here we may have admitted a confusion not dealt with clearly in the target article in section 4.8. Our proposal that the parahippocampal region was critical to intermediate-term storage of individual items did not, we tried to argue, preclude critical hippocampal mediation in intermediate-term memory when the material to be stored involves the establishment of a relational representation. For example, animals with hippocampal damage should, and indeed do, show rapid forgetting in delayed nonmatch to sample when the item to be stored is a "place." We would also expect critical hippocampal mediation in the maintenance of memories for items with nonspatial relations. Thus, for example, we include within the domain of relational representations the kinds of memory organization that involve the ordering or relative recency of items. As predicted, animals with hippocampal damage also show rapid forgetting of the relative recency of experiences in nonspatial working memory tasks and DRL (see sects. 4.4 and 4.9). Kesner should be content to hear we have not taken "time," in the broad sense, out of the hippocampus. What does not require hippocampal function, we argue, is the maintenance of representations for individual items, those that are not temporally or otherwise "tagged" within a broader organizational context.

Kesner has also raised the problem that the decay of memory for spatial or temporally tagged information is virtually immediate in animals with hippocampal damage. This fits very nicely with our view that the hippocampus itself mediates the very establishment of relational representations. To the extent that memory would rely on such a representation, none is established in the absence of hippocampal function, and therefore the critical representation is not created even at the outset of a delay.

R2.6. Is spatial special? The popular notion that spatial relations may be "special" in the evolution of hippocampal function is shared by **Bingman** and **Nadel.** We do not doubt Bingman's point that the development of brain structures probably follows evolutionary demands, and that demands for migration, catching, or other spatially defined behaviors might have been sufficient to drive the development of the hippocampal system. It is notable that if Bingman is right for those data, the fact that other data indicate that the hippocampal system processes other relations "beyond space" suggests that spatial mapping is just a subset of relational capacities the hippocampus may support once evolved. In addition, although some of the studies on the size of the bird hippocampus attempt to provide good controls for a specific evolutionary demand for spatial relational processing (see Bingman), and although we are in no position to refute this, it is likely that closely related birds with different spatial ranges for hoarding differ in other ways as well. The conclusion that a specific demand exists for spatial mapping is based solely on correlational findings – hence any number of other nonspatial factors could account for these data. Let us suggest one. Concurrent with the demand for spatial mapping in wide-ranging animals there might be a demand for several other applications of relational memory, such as the organization of social affiliations, learning which foods are appropriate for particular locales, or learning which kinds of trees are good to hide in, mate in, or play in. The point is that there are a lot of ways it might be handy to have an organization of memories, especially if one's habitat is large.

With regard to **Nadel's** preference for the spatial mapping theory, we may or may not be very close in our characterizations of hippocampal function, depending on just what he means by a "cognitive map." In the original

characterization of cognitive mapping, the proposal was that the hippocampus mediates the organization of allocentric space, constructing and storing a more or less literal map of geographic relations among objects in the physical environment. However, when confronted with data that demand an extension beyond this limited domain, the theory has suffered from just the sort of "hypothesis drift" of which Nadel accuses others. Thus, when in the purist mode, the claim is that "We were referring to space, and we meant space, not abstractly, but concretely." (Nadel 1991, p. 228). But when convenient, the cognitive map notion has been extended to situations as diverse as "spatio-temporal contexts" (Nadel 1991; Nadel & Wilner 1980), Gaffan and Harrison's (1991) "scenes," and human declarative memory (see Nadel 1991), none of which are restricted to allocentric spatial mapping. Eventually (and we hope this exercise nudges him in the right direction), there will be enough drift to arrive at "conceptual" rather than "physical" space, and we may have no disagreement at all. Most important, though, is that we should not focus our effort on whether the hippocampus mediates conceptual space or geography. The really interesting insights to be found in *how* (spatial or nonspatial) relational representations are organized in support of the representational flexibility unique to this memory system. Only when Nadel, Bingman, and other adherents of the spatial mapping hypothesis perform the same kind of probe testing we have used to give some flesh to the model, can we fully evaluate the merits of their proposal; we have put our theory up to a higher standard of evaluation.

R2.7. An updating on our concept of the role of the parahippocampal region: Cue compression as intimately associated with intermediate-term storage. We appreciate the commendations from **Brown** and **Horel** for placing greater emphasis on the parahippocampal cortical areas than previous proposals. We too think this broad area deserves greater experimental and conceptual attention, which we will offer now. To this end, new conceptual models (**Gluck et al.**) and our own new data (cited by **Murray** and **Jarrard**) have helped sharpen our views on the functional role of the parahippocampal region. More specifically, a combination of a proposal by Gluck and colleagues and data on the effects of parahippocampal and hippocampal lesions on paired associate learning (Bunsey & Eichenbaum 1993a; 1993b; Murray et al. 1993) have led us to extend our views on the function of the parahippocampal region. We now propose that the intermediate-term storage of items in the parahippocampal region permits the "compression" of representations of separately presented stimuli into conceptually fused items in memory. Notions like our "cue compression" have occurred several times to account for how the "binding" of associations might be accomplished. William James (1890) referred to the conceptual "fusion" of cues that are to be closely associated. In his studies of amnesic patients, Schacter (1985) distinguished impaired explicit learning from the intact ability to use associations in the form of a "unitized structure," which he characterized as "a discrete memory representation that can be activated in an all-or-none manner and that behaves as a cohesive, integrated whole." Sutherland & Rudy (1989) characterized configural association as accomplished when "the stimulus controlling behavior consists of a unique neural representation constructed from the combined representations of elementary stimuli." Thus we now further emphasize our view of the parahippocampal region as a supramodal association cortex for the conventional neocortical association areas and suggest that its job is to converge the distinct representations sent from these areas and combine them into conceptual composites.

It is important to note that the intermediate-term memory function of the parahippocampal region is intimately associated with cue compression, in that an extended holding capacity may be used to combine representations that occur separately in time. Thus, items appearing even seconds apart may be compressed into a single representation if, to use Gluck and colleagues' term, the items are "redundant," that is, their combination is predictive. Schacter's characterization of unitized structures as applying to idioms is a particularly good example of cue compression here. Words that compose idioms occur separately in time and are independently meaningful, but the meaning of the idiom can be virtually unrelated. For example, the meaning of "sour grapes" has nothing to do with taste or fruits.

Cue compression is a powerful way to "bind" stimulus associations, but it is also quite limited in its representational flexibility. Thus, compressed representations are powerful in that they can be used to disambiguate the compound cues whose elements have multiple conflicting consequences (Sutherland & Rudy 1989). However, as Schacter characterized it, unitized representations are "hyperspecific," in that, unlike relational representations, they cannot be used flexibly when the elements are separated or rearranged. Our own experiments have emphasized this point. Animals with damage to the hippocampus sparing the parahippocampal region sometimes resort to inflexible compressed representations to solve problems (Eichenbaum et al. 1991).

R2.8. Distinguishing cue compression and relational representation: The danger of confusion. Our distinction between cue compression by the parahippocampal region and relational representation by the hippocampal formation requires further elaboration if we are to avoid confusion about different ways to "bind" stimuli in memory, as exemplified by the comments of **Jarrard, Good & Morris, McNaughton,** and **Murray.** In particular, our notion of "compositionality," which we claim characterizes relational representation mediated by the hippocampal formation, emphasizes the distinctness of perceptually and conceptually independent cue elements while organizing these representations according to the relevant relationships (see sect. 4.5). By contrast, "compressed" representations that we propose occur in the parahippocampal region do not maintain the individuality of the elements. Rudy and Sutherland's (1992) proposal does allow for separate representations of both the cue elements and the configural (compressed) representation, but each of these merely enters into associations with each other and with other items (e.g., rewards) – this framework does not support different types of relations among the elements.

It is important to realize that the distinction between the functions proposed for the parahippocampal and hippocampal areas are something greater than "orthogonal,"

as proposed in the target article. We now see these areas as "antagonistic," in the sense that cue compression and relational representation are two opposing ways to represent multiple cues. Thus, entirely consistent with **Gluck et al.**'s model, we view the parahippocampal region and hippocampal formation as competing to represent multiple cues either by compressing them into unitized configurals or by differentiating and organizing them according to their relationships, respectively. This construal of the interplay between the parahippocampal cortical areas and hippocampal formation may please **McNaughton** who, as we read his commentary, seems to see the hippocampus as a relational "antiprocessor" inhibiting the formation of compressed representations by the cortex.

There is a strong danger of confusing cue compression and relational representation. We believe, for example, that Sutherland and Rudy have so far failed to come to grips with this distinction in sorting out the findings on what they call configural learning. The mixture of data on various tasks, we believe, may be due to the occasional success of animals with damage to the hippocampal formation but intact parahippocampal areas in solving compound discrimination problems by compressing stimuli into configural cues. Of course, only appropriate probe tests of the form described above can tell us whether configural or relational representations were used in any particular paradigm.

Good & Morris misunderstood our interpretation of the probe test data on simultaneous odor discrimination, confusing relational and configural representations. We found that when rats with hippocampal formation damage occasionally succeeded at simultaneous odor discriminations, they did so by encoding the odors as unitized stimulus compounds – our probe tests showed that their representation could not support recognition of the familiar odors in novel rearrangements that mispaired odors from different discrimination problems. Thus, our interpretation was precisely that the rats had resorted to configuring to solve each problem, but that their way of binding the odors did not support individual identification of the same odors in the probe tests. To us, the implication was that normal rats succeeded in identifying odors in novel rearrangements because they had formed a relational representation including all the odors, and the compositionality of this representation allowed them to compare and contrast the elements presented within or across problems. Contrary to our view, Morris accuses normal rats of being so representationally impoverished as to have only the capabilities of amnesic rats. We give normal rats more credit, and suggest that credit be given to us for this correct experimental prediction.

The most compelling support for our view of antagonistic parahippocampal and hippocampal forms of representation comes from the emerging data on paired-associate learning cited by **Murray** and **Jarrard.** Because the recall method commonly used in paired-associate testing in humans cannot be directly applied to animals, variants of this task in animals require that the subject discriminate between assigned cue pairs and inappropriate pairings of the same items. Given this design, the task can be accomplished in at least two ways, one in which the two cues presented in each unique stimulus sequence are "compressed" into a unitized representation and the other in which each stimulus representation is held separate and organized according to the assigned pairing composition. Our initial findings using this task indicated that the parahippocampal area attempts to perform the cue compression while the hippocampal formation is competing to form the relational representation. We trained rats to discriminate sequentially presented odor pairs from mispairings and found that removal of the parahippocampal region resulted in a severe impairment (Bunsey & Eichenbaum 1993b). Conversely, we found that neurotoxic ablations of the hippocampal formation resulted in a facilitation of this type of paired-associate learning (Bunsey et al. 1993b). In interpreting this pattern of results, it is initially important to recognize two general indications: first, both the parahippocampal region and the hippocampus are implicated in normal paired-associate learning. Second, this pattern of results suggests that these structures participate through antagonistic mechanisms. Our account of these data is that, in normal animals, the hippocampal relational representation normally "wins out" over the parahippocampal cue compression. However, when the hippocampus is damaged, the parahippocampal region successfully mediates acquisition through a cue compression. When the parahippocampal region is ablated, the task cannot be performed by cue compression, and this lesion cuts off the possibility of hippocampal mediation, so neither representational strategy remains. Our proposal that the parahippocampal region and the hippocampal formation mediate antagonistic representations of paired associates resolves Murray's contention that our analysis fails to explain the data, and it offers a much richer formulation of the functions of these two components of the hippocampal system. A confirmation of this account of paired-associate learning awaits probe tests currently under investigation; meanwhile, it is worth noting that Saunders and Weiskrantz (1989) found that monkeys with hippocampal formation damage sparing the parahippocampal region succeeded in learning closely spaced object paired associates but, unlike normal monkeys, they failed to recognize the pairing relations when the objects were separated – a finding precisely predicted by our account.

One final point: according to this account of our data on paired-associate learning, the acquisition of a relational representation, although normally successful in intact animals, was slower (in rats) or no better (in monkeys) than the acquisition of the task by cue compression. This curious conclusion suggests that there is little to be gained by a relational representation, at least for this sort of paired-associate learning. We suggest that this may indeed be the case in situations where the stimuli and context of learning are as artificial as that used in all these experiments. Some results from studies on a "natural" form of paired-associate learning by rats are consistent with this view. Galef (1990) has shown that rats learn from conspecifics which foods are preferable by experiencing the pairing of a distinctive (not necessarily novel) food with an odorous constituent of rat's breath (carbon disulfide). This form of paired-associate learning is severely impaired after conventional hippocampal ablation (Winocur 1990) and we have recently shown it to be blocked by selective neurotoxic lesions of the hippocampal formation (Bunsey & Eichenbaum 1993b). So, sometimes the learning of paired associates *does* depend on the hippocampal formation. But there are, perhaps, two more compelling

take-home messages from these results. First, the findings show that learning nonspatial stimulus relationships in a "natural" context (one that should satisfy **Nadel** and **Bingman**) depends on the hippocampal formation. Second, and more generally, our notions about cue comparison and relational representation offer different solutions to the "binding problem" in memory and suggest that they may be accomplished by separate brain structures. This account, focused on the interplay of components of the hippocampal system and based on explorations of memory representation, suggests that a resolution to that long standing issue may be emerging from endeavors in cognitive neuroscience.

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Letters *a* and *r* appearing before authors' initials refer to target article and response respectively.

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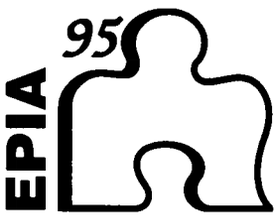

EPIA'95 — CALL FOR PAPERS

SEVENTH PORTUGUESE CONFERENCE ON ARTIFICIAL INTELLIGENCE

Funchal, Madeira Island, Portugal
October 3-6, 1995

(Under the auspices of the Portuguese Association for Artificial Intelligence)

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Deadlines
Papers due: March 20, 1995
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Papers returned: June 12, 1995

Official Language
English

The Seventh Portuguese Conference on Artificial Intelligence (EPIA'95) will be held at Funchal, Madeira Island, Portugal, on October 3-6, 1995. As in previous issues ('89, '91, and '93), EPIA'95 will be run as an international conference, English being the official language. The scientific program encompasses tutorials, invited lectures, demonstrations, and paper presentations. Five well known researchers will present invited lectures. The conference is devoted to all areas of Artificial Intelligence and will cover both theoretical and foundational issues and applications as well.

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