

Hippocampal System and Declarative (Relational) Memory: Summarizing the Data From Functional Neuroimaging Studies

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ABSTRACT: In the last several years there have been impressive strides in the ability to explore the nature of hippocampal system functioning in humans by employing functional neuroimaging methods, permitting such methods to be used in conjunction with neuropsychological methods to better understand the role of the hippocampal system in memory. In this paper, we review the literature on functional imaging studies of the hippocampal system, summarizing the data and testing these data against a number of theories or explanatory accounts of hippocampal function. We consider five alternative explanatory accounts of, or ideas about, hippocampal function—some from already existing work, for which the functional imaging data can provide a new test, and others that have emerged directly from the functional imaging work, and that have yet to be tested for their fit of data from neuropsychological methods. We conclude that the relational (declarative) memory account, in which it is proposed that the hippocampal system plays a critical role in binding together multiple inputs to permit representations of the relations among the constituent elements of scenes or events, can better accommodate the full range of imaging (and other existing) data than any other explanatory account of hippocampal function. *Hippocampus* 1999;9:83–98.

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INTRODUCTION

Ever since the original report of profound and pervasive amnesia following medial temporal-lobe resection in the patient H.M. (Scoville and Milner, 1957), there has been an enormous amount of research aimed at characterizing the nature of amnesia and the functional role in memory of the hippocampal system, both in humans and in animals (for reviews see Squire, 1992; Cohen and Eichenbaum, 1993; Eichenbaum et al., 1994). This research has availed itself, over the years, of all currently available methods, including neuropsychological studies of patients with brain

injuries or of animals with experimental lesions, and single cell recordings in animals or surface recordings in humans performing various memory tasks. When functional neuroimaging techniques (especially positron emission tomography [PET] and functional magnetic resonance imaging [fMRI]) provided new methods with which to assess activity in hippocampal regions in human subjects engaged in various memory performances, it was inevitable that they too would be applied to this issue. The last several years have seen a rapidly growing number of functional imaging studies of the human hippocampal system, and with it a growing amount of (often conflicting) information about its functional role in memory.

In this paper, we review the literature on functional imaging studies of the hippocampal system, summarizing the data and testing these data against a number of theories or explanatory accounts of hippocampal function. The first several years of functional imaging research on memory produced very few successes in “activating” the hippocampal system, but in more recent years there has been a series of successful studies. As is often the case when new methods are introduced, the functional imaging data differ greatly in the extent to which they align with already extant data from more classical (in this case, neuropsychological) methods. These issues are discussed at the outset of this paper. We then turn to a brief discussion of a number of alternative explanatory accounts of, or ideas about, hippocampal function, some from already existing work, for which the functional imaging data can provide a new test, and others which have emerged directly from the functional imaging work, and which may or may not be able to accommodate data from neuropsychological or other methods. Five of the most visible such accounts will be discussed here. Finally, in the major section of this paper,

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we explore the fit of the functional imaging data to these various explanatory accounts.

EARLY FINDINGS: THE RECALCITRANT HIPPOCAMPUS

The early attempts to see hippocampal activation in PET or fMRI were largely disappointing, as perhaps best summed up by Aquirre et al. (1996): “the hippocampus has been a recalcitrant target of functional neuroimaging studies.” The difficulty in finding hippocampal activation was commented upon in many of the early papers, leading authors to speculate on various possible difficulties in imaging the hippocampal region. One set of concerns raised the possibility that it just wasn’t going to be possible to image the medial temporal-lobe region in action, because of: problems of susceptibility artifacts in that portion of the brain when imaging with fMRI methods; or concerns about the likelihood of too-small a range of hemodynamic change in the medial temporal lobes compared to, say, cortical processing regions; or the possibility that memory encoding or representation by the hippocampal system is so *sparse* (i.e., circumscribed in the portion of the hippocampal network engaged by any given learning event) that it would produce only vanishingly small activations. A very different set of concerns related to the possibility that functional imaging required different paradigms than the ones used in neuropsychological work and/or different conceptualizations of the nature of memory processing accomplished by the hippocampal system. Whereas the first set of concerns, if borne out, would prevent functional imaging from helping to inform the debate about memory and the hippocampal system, the second set of concerns raised the possibility that results forthcoming from neuropsychological studies and results arising from functional imaging studies would fail to converge on a common view of the role of the hippocampal system in memory, bringing those literatures into fundamental conflict.

The number of reports of hippocampal activation in various memory tasks that have been published in the last few years serves to dispel the first set of concerns. The human hippocampal system can be seen in action during the performance of various memory tasks, after all, thereby providing us with an additional tool with which to explore the brain bases and the functional organization of memory. However, the extent to which interpretations of various functional imaging studies can be successfully aligned with interpretations of neuropsychological (and other) studies, or, for that matter, can be aligned with one another, still needs to be addressed. The possibility of lack of concordance of functional imaging and human neuropsychological data, and the questions it raises about the suitability of the paradigms derived from the studies of amnesia for use in functional imaging, bears considerable resemblance to similar issues that were raised in early work with animal models of amnesia. There, as here, the early studies failed to align (for review see Cohen and Eichenbaum, 1993). However, the major claim of the current paper is that they do

indeed converge, together with other lines of evidence, on a common view of the role of the hippocampal system in memory.

“HIPPOCAMPAL SYSTEM”: HIPPOCAMPUS VS. PARAHIPPOCAMPAL REGION

Before going any further, it is important to clarify the issue of what constitutes “the hippocampal system” and how integrated or unitary a “system” it is. The term hippocampal system is meant here to include the hippocampus and related medial temporal-lobe structures that when damaged, as in the patient H.M., cause memory impairment. Current work on human amnesia and animal models of amnesia indicates that in addition to the hippocampus itself, the overlying cortical areas—the entorhinal, perirhinal, and parahippocampal cortices—play a critical role in memory and amnesia (e.g., see Eichenbaum et al., 1994; Zola-Morgan, 1995; Murray, 1996). As in Eichenbaum et al. (1994), we refer here to those cortical areas collectively as the parahippocampal region. Recent work in the field has distinguished its anatomical and functional properties from those of the hippocampus itself. However, it is generally believed within the neuropsychological and animal literatures that the various components of the hippocampal system contribute to the same *kind* of memory, even if their precise processing contributions differ. Hence, questions about the functional role of the hippocampal system as a whole, certainly in terms of the domain of memory mediated by the hippocampal system, can be addressed.

Although functional imaging would seem to hold considerable promise for disentangling the roles of various components of the hippocampal system, the state of this literature suggests that there is considerably more work to be done on this particular front. Many functional imaging studies have presented data from medial temporal-lobe structures globally, particularly in the older PET studies, and thus do not permit readers of this literature to distinguish activity in hippocampus from activity in parahippocampal areas. Some of the more recent studies have reported separately on the extent of activity in hippocampus vs. the parahippocampal area, but sometimes couch the presentation of data in language such as “...in the vicinity of the hippocampus.” Finally, even in recent writings concerning possible anterior-posterior differences in hippocampal activation as a function of type of memory demands, the possibility that anterior vs. posterior may be (at least in part) confounded with hippocampus vs. parahippocampal area has not been addressed. Unfortunately, in general, in evaluating this literature it is not always clear (1) if the investigators analyzed activity in hippocampus and the parahippocampal area separately, (2) if they had the capability necessary (i.e., high enough spatial resolution and signal-to-noise) to successfully distinguish between these regions, and (3) if the different components of the hippocampal system are equally amenable to being assessed with functional imaging techniques.

It is important to keep in mind that the parahippocampal region receives and operates upon input from higher-order visual (and other sensory) processing areas, and that information arriving there will therefore elicit significant processing whether or not the hippocampus ends up being significantly engaged. It may be for this reason that there are far more reports of parahippocampal activation than of hippocampal activation in the literature. And, to anticipate a point that will emerge later in this paper (in the section on Novelty), parahippocampal activity may at times be more related to processing within the visual (or other sensory) processing stream(s) than it is to processing within the hippocampal system; i.e., more related to high-level stimulus analysis or manipulation than to memory processes.

In the review of the literature, below, we occasionally distinguish hippocampus and the parahippocampal area, but most often treat the data collectively as reflecting the participation of the hippocampal system for purposes of attempting to understand the domain of memory for which the system operates. Recently, there have emerged efforts to distinguish among components of the hippocampal system with respect to their roles in encoding vs. retrieval of memory, exploring the possibility, for example, that anterior and posterior portions of the hippocampal system differ with regard to the stage of memory processing in which they are involved (see Gabrieli et al., 1997; Lepage et al., 1998; see Schacter and Wagner, and other papers in this volume). But, as was the case with the neuropsychological work on memory and amnesia, discussions of the participation of the hippocampal system in encoding vs. retrieval operations is orthogonal to the issue of what is the domain of memory for which the hippocampal system operates, and hence will play little role in this review.

CONCORDANCE WITH NEUROPSYCHOLOGICAL FINDINGS?

One goal of the present review, and a major tenet of cognitive neuroscience in general, is to look for convergence of findings from the various methods used to explore the brain bases of memory (or whatever cognitive capacity is under study). As alluded to above, the failure of early functional imaging studies to observe hippocampal system activity during the performance of various memory tasks—the very kinds of memory tasks on which patients with hippocampal system damage are impaired—threatened a lack of concordance between functional imaging and neuropsychological findings as to the functional role of the hippocampal system. More recent functional imaging work has proven more successful, reporting hippocampal activity in a variety of tasks. But are interpretations of the findings from the two methods concordant with one another? A cursory look at the emerging functional imaging literature reveals a variety of claims about the nature of hippocampal function, some of them clearly at odds with those from the literature on memory and amnesia. We take as our charge here to see if a deeper analysis of these findings can find significant convergence, after all.

One place to start in looking for concordance concerns the range of to-be-remembered materials over which the hippocampal system operates. Studies of the patient H.M. and other patients with bilateral damage to the hippocampal system have shown that amnesia is a *global* memory deficit. Such patients have a material- and modality-general impairment, encompassing verbal and nonverbal, spatial and nonspatial materials, regardless of whether they are presented visually, auditorily, etc. (e.g., see Milner and Teuber, 1968), indicating that the hippocampal system's role in memory is, likewise, *nonspecific* with regard to material and modality (see Cohen, 1997). At the same time, studies of patients with unilateral damage to the left or right medial temporal-lobe region have shown clear material-specific memory impairments: Verbal and nonverbal memory performances are selectively compromised after medial temporal-lobe damage in the left and the right hemisphere, respectively (e.g., see Milner, 1971, 1972). Thus, there is a laterality to the hippocampal contribution to memory, corresponding to the kinds of processing for which the hemispheres are specialized. The question here is how well do the findings from functional imaging studies of memory correspond to this picture from neuropsychological studies?

Across a variety of functional imaging studies we can see both the globalness of hippocampal processing, when considered bilaterally, and also the material-specificity of left vs. right hippocampal system processing. Two recent studies addressed this question directly, illustrating nicely the hemispheric specializations. In addition, taking together results from various other studies, the global scope of hippocampal processing is seen clearly, extending across a wide range of different materials. An fMRI study by Kelley et al. (1998) involved presenting subjects with words, nameable line drawings of objects, and unfamiliar faces in separate blocks, with instructions to study the items for a later memory test. We found that, compared to a condition involving passive viewing of a fixation point, significant hippocampal activation occurred in all three encoding conditions, and it varied by hemisphere as a function of the materials being studied: Words produced predominantly left hippocampal activation, nonfamous faces elicited predominantly right hippocampal activation, and nameable line drawings resulted in bilateral hippocampal activation. A second experiment in that report tested passive viewing of the three classes of stimuli compared to the fixation point condition, and basically replicated the findings of the first experiment. A similar PET study Martin et al. (1997) tested viewing of objects, words, or nonsense words in separate blocks, compared to visual noise patterns, again finding hemispheric differences in the type of material processed by the hippocampus: Compared to viewing visual noise patterns, viewing of objects produced more right hippocampal activity than left, whereas viewing words elicited more left hippocampal activity than right. Additionally, the preferential activation of the left hippocampal system for words was greater for real words than nonsense words.

Looking across the range of studies successfully observing hippocampal system activation, we see how broad a range of stimulus materials can engage this system. Ignoring now which hemisphere is disproportionately activated, hippocampal activation has been reported for words (Martin et al., 1997; Kelley et al.,

1998; Wagner et al., 1998), objects (Schacter et al., 1995, 1997; Kanwisher et al., 1996; Martin et al., 1997; Kelley et al., 1998), scenes (Tulving et al., 1994b; Stern et al., 1996; Gabrieli et al., 1997; Montaldi et al., 1998; Brewer et al., 1998), faces (Sergent, 1992; Grady et al., 1995; Kapur et al., 1995; Haxby et al., 1996; Kelley et al., 1998), spatial routes (Maguire et al., 1997), and landmarks or locations (Maguire et al., 1997; Aguirre and D'Esposito, 1997). Taken together with the studies noted above, these functional imaging data correspond well with the neuropsychological data regarding materials. Given this concordance, we can move with more confidence to our analysis of what the imaging data suggest about the domain of memory supported by the hippocampal system.

EXPLANATORY ACCOUNTS OR IDEAS ABOUT HIPPOCAMPAL FUNCTION

We turn now to consideration of a number of alternative explanatory accounts of, or ideas about, hippocampal system function. We cannot consider all of the various published ideas about hippocampal function in the space allotted here, so we will focus on five of the most visible such accounts. Three of these come from work using methods other than functional imaging, in particular work on human and animal amnesia, and which have been hugely influential in that literature and influential as well in the design of the functional imaging studies, as we shall see. The other two ideas about hippocampal function to be considered here have instead emerged directly from functional imaging, offered to describe and explain particular imaging data. The five accounts are the following:

1. novelty
2. retrieval success
3. explicit (vs implicit) memory
4. spatial (cognitive) mapping
5. relational memory processing (declarative [vs procedural] memory)

Here we offer brief descriptions of these various ideas. Having introduced them in this section, we move on in the next section to explore in detail their ability both to handle the full range of imaging data and to accommodate data from neuropsychological or other methods.

Novelty

Based on the finding in a PET study of (right) limbic system activation for novel items compared to previously studied items, Tulving et al. (1994b) proposed that the hippocampal system is part of a "novelty encoding network" in the limbic system. On such a view, the role of the hippocampal system in memory includes detecting novel stimuli and encoding information about those stimuli in memory.

Retrieval Success

Impressed by correlation between memory test performance and hippocampal activation in their PET study, Nyberg et al. (1996) proposed that the hippocampal system is involved in the successful retrieval of previously stored information; i.e., in the reactivation of stored representations.

Explicit (Vs. Implicit) Memory

Graf and Schacter (1985) proposed the widely noted distinction, based on performance dissociations in normal subjects and amnesic patients, between explicit memory, involving conscious recollection of some prior study episode, and implicit memory, in which the effects of previous experience can be manifested without requiring gaining conscious access to any specific experience. It is suggested that the hippocampal system plays a critical role in explicit memory.

Spatial (Cognitive) Mapping

Based initially on data from recordings of hippocampal neurons and on behavioral deficits arising from hippocampal lesions in rats, O'Keefe and Nadel (1978) proposed the well-known view that the hippocampal system plays a crucial role in spatial memory, permitting the ability to construct, maintain, and make use of spatial maps of the environment.

Relational Memory Processing (Declarative [Vs. Procedural] Memory)

Based on the distinction we proposed between declarative and procedural memory, to account for the pattern of impaired vs. spared memory performances in (human and animal) amnesia (Cohen and Squire, 1980; Cohen, 1984; Squire, 1992; Cohen and Eichenbaum, 1993), it is proposed that the hippocampal system is critically involved in memory binding or relational memory processing—binding the converging inputs from various processors, permitting it to mediate representations of the relationships among the constituent elements of scenes or events (Cohen and Eichenbaum, 1993; Eichenbaum et al., 1994).

SUMMARIZING THE FUNCTIONAL IMAGING DATA: ASSESSING THE FIT OF THE DATA TO THE VARIOUS EXPLANATORY ACCOUNTS

How well do these alternative accounts handle the full range of imaging data? Can the data from the emerging functional imaging literature be handled by one or another of the already existing theories of hippocampal function, or do these data require new accounts? How well do the functional imaging data align with findings from neuropsychology and other methods? These questions are addressed by assessing the fit of the imaging data to each of the five proposed accounts, in turn. For each of the proposals

about hippocampal function we (1) indicate how it was introduced or first applied to imaging data, (2) then we look to the full range of the imaging literature to find data that we believe can be used (or perhaps reconceptualized) to provide support for such a view, and (3) finally we point out other data from the literature that we believe cannot be handled well and thus argue against that particular view. This is done both in the text and in a summary table accompanying each section (see Tables 1–5).

Novelty

Account of hippocampal function

Tulving et al. (1994b) proposed that there are novelty encoding networks in the brain responsible for detecting novel stimuli and encoding that information in memory, and that the limbic system, including especially the hippocampal system, is a critical part of that network. Accordingly, the hippocampal system is seen as being systematically and disproportionately engaged for the processing of novel as compared to already familiar materials.

Initial application to imaging

This idea comes from a PET study by Tulving et al. (1994b), in which subjects viewed scenes (taken from old *National Geographic* magazines) twice prior to scanning, and then 24 hours later viewed these “old” scenes and “new” ones while being scanned. In each block, the scan window consisted of either old or new scenes exclusively, although the beginning and end of each block contained both old and new scenes. Subjects were informed before each scan whether the majority of the items they were about to see would be old or new, and were instructed to count the oddballs. Greater activation in the new-old subtraction was observed in various right hemisphere limbic structures, including particularly the hippocampal system.

Data supporting this account

While the Tulving et al. (1994b) report makes perhaps the strongest case for the novelty idea, we can find at least two other lines of work that would seem to provide further support. In an fMRI study by Stern et al. (1996), color scenes (magazine photos) were again the stimuli. Subjects viewed the scenes in alternating experimental and control blocks, in which either a series of different scenes was presented once (experimental) or just one scene was presented repeatedly (control). They were instructed to study the scenes so that they might be able to recognize them later, and they were scanned during this study phase. Greater activation was seen in (posterior) hippocampal regions for the novel scenes in the experimental condition compared to the single repeated scene in the control condition. In Kanwisher et al.’s (1996) fMRI study, subjects viewed nameable objects, faces, hands, houses, and scrambled faces. Greater hippocampal activation was observed bilaterally for objects than for faces. We take this as relevant to the novelty idea because the series of studies conducted in this report resulted in the faces being repeated across various tests, making them less novel than the objects.

TABLE 1.

Novelty Account of Hippocampal Function

Account of hippocampal function

Part of novelty encoding networks in [right] limbic system

Initial application to imaging

New > old scenes (Tulving et al., 1994b)

Best case for account

New > old scenes (Tulving et al., 1994b)

Other data in favor

Varied > repeated single scenes (Stern et al., 1996)

Less frequent objects > more frequent faces (Kanwisher et al., 1996)

But

Activation for old items > new items

Studied > new possible objects (Schacter et al., 1985, 1987)

Famous & repeated nonfamous > novel nonfamous faces (Kapur et al., 1995)

Activation differs across conditions that are equally novel

Associative > perceptual processing of scenes (Montaldi et al., 1998)

Interactive > Independent encoding of face-house stimuli (Henke et al., 1997)

No activation

No activation for all novel vs half novel word stems (Buckner et al., 1995)

No activation for new vs old sentences (Tulving et al., 1994a)

Data not handled by this account

We see three classes of findings as providing difficulty for the novelty view (see Table 1). The first set of findings are cases in which greater hippocampal activation was found for old vs. new items, a pattern opposite to what was predicted in the novelty account of hippocampal system function. Schacter et al. (1995, 1997) explored memory for possible and impossible (line drawings of) objects in two PET studies. Subjects were scanned while they made either possible/impossible or old/new recognition judgments to previously studied vs. novel objects. Both of these conditions produced hippocampal activation bilaterally compared to a no-decision baseline condition, for both old and new possible objects, showing more activation for repeated than for novel possible objects. In Kapur et al. (1995), subjects performed a gender identification on nonfamous faces, an anterograde memory task with nonfamous faces (judging which faces had vs. had not been presented previously), and a politician classification task with famous faces. The two conditions involving previously seen faces—famous faces or repeated nonfamous faces—both produced more (left) hippocampal activation in PET than the gender identification condition involving nonrepeated nonfamous (i.e.,

novel) faces. Again, prior exposure led to greater, not less, hippocampal activation.

A second line of work that cannot be handled by the novelty account concerns findings of differences in hippocampal activation across conditions in which there was no difference in novelty. Montaldi et al. (1998) showed subjects old *National Geographic* photos in their SPECT study, and had them either perform an associative encoding task (in which they were to focus on what the picture was about, how the features related to each other within the picture, and the spatial locations of items) or a perceptual matching task (in which three photos were shown and subjects were to match the top with one of the other two, being warned that there was a high degree of similarity in the theme of the choices and any attention paid to the theme would not help). Greater (left) hippocampal activation was found for the associative encoding condition compared to the perceptual matching condition for the same photos. In this case, as in the related Henke et al. (1997) PET study discussed in a subsequent section, the novelty idea can offer no account of the variance in hippocampal activation across conditions that use identical stimuli.

A third class of findings that we see causing difficulty for the novelty account involves experiments that systematically vary novelty across conditions but fail to observe differential hippocampal activation. Buckner et al.'s (1995) series of PET studies involved comparing conditions in which subjects were presented word stems (the initial few letters of words) of which half could be completed to words that had been on a pre-scanning study list vs. conditions in which subjects were presented with stems that completed only novel (non-studied) words. No hippocampal activation was reported. Likewise, Tulving et al. (1994a) had subjects listen to sentence frames and semantically-related words, with the task of rating the meaningfulness of each sentence. Twenty-four hours later, subjects listened to old and new sentences while in the PET scanner. During the scan window all sentences were either old or new, although the beginning and end of each block consisted of both old and new items. Subjects were told before each scan whether the majority of the sentences would be old or new and were instructed to count the oddballs. These conditions replicate the Tulving et al. (1994b) study discussed above, using sentences rather than scenes. But here no hippocampal activation was found for the new-old comparison.

This third class of findings, involving a failure to observe the predicted effect of novelty, should be tempered by the fact that there are always multiple reasons why one may fail to see a predicted result, for methodological or statistical reasons, for example. This is particularly so when no hippocampal activation was seen in *any* condition. But, together with the above-mentioned examples of studies reporting differential hippocampal activation across conditions of equal novelty, and of studies reporting patterns of hippocampal activation opposite to those predicted (an *anti*-novelty effect), both constituting instances of hippocampal activation occurring in the wrong conditions, it is clear that the novelty idea cannot handle the full range of imaging data.

There is one final concern regarding the novelty idea that we have not seen discussed elsewhere in the literature. A variety of

previous studies have shown that cortical visual processing regions show diminished activation levels for materials that have been repeated (for review see Buckner et al, 1998); i.e., more activation for novel than for repeated stimuli. To the extent that the parahippocampal region may be closely tied to the sensory processing streams that provide input to it and hence related to high-level stimulus analysis or manipulation rather than to memory processes, an idea we raised earlier in this paper, at least some of the "hippocampal system" activation reported for novel vs. repeated items may be the same sensory system *priming* that is seen in extrastriate cortex and other cortical processing areas.

Contact with neuropsychological and other findings?

Studies of amnesia show that although hippocampal damage does impair the ability to distinguish novel from repeated items (as evidenced, say, in impaired recognition memory or delayed match-to-sample task performance), and hence that the hippocampal system may be considered a necessary element in detection of novelty, the memory impairment extends well beyond novelty detection. Amnesic patients are profoundly impaired at learning arbitrary relations among items even when they are repeated over and over, showing deficits in paired-associate learning (of arbitrary pairings of words), learning face-name pairings, or learning vocabulary, i.e., word-meaning pairings (see Cohen et al., 1997). Findings from recordings of hippocampal neurons are also outside the scope of the novelty account. Just consider the well-known findings of "place fields" in which particular hippocampal neurons fire reliably whenever the animal is in one or another particular "place" in its environment (e.g., O'Keefe, 1979; McNaughton et al., 1983). The place fields develop with exposure to the environment and then remain constant as the animal navigates through the familiar space, long after that environment has lost whatever novelty it may have possessed. Accordingly, the novelty idea has little explanatory power outside of the functional imaging data, thereby providing an independent reason to argue against it as a full account of hippocampal function.

Retrieval Success

Account of hippocampal function

Nyberg et al. (1996) proposed a critical role for the hippocampal system in the successful retrieval of previously stored information, arguing that it is involved in the reactivation of stored representations. They speculated that successful reactivation results in the brain regions involved in memory storage sending feedback to the medial temporal area, causing increased hippocampal activation. Accordingly, the hippocampal system is seen as being systematically and disproportionately involved during successful as compared to unsuccessful memory performance.

Initial application to imaging

This idea comes from a PET study by Nyberg et al. (1996), in which subjects listened to two lists of words prior to being in the scanner. For one list subjects were to decide whether each word

TABLE 2.

Retrieval Success Account of Hippocampal Function

Account of hippocampal function

Involved in the successful retrieval [reactivation] of stored representations

Initial application to imaging

Semantically > perceptually encoded words; correlation between retrieval and activation (Nyberg et al., 1996)

Best case for account

Semantically > perceptually encoded words; correlation between retrieval and activation (Nyberg et al., 1996)

Other data in favor

Memory > gender judgments for faces (Kapur et al., 1995)

But

Differences in activation across conditions that all involve successful retrieval

Retrieval of routes > landmarks, movie plots, movie scenes (Maguire et al., 1997)

Activation for new items compared to studied items

New > old scenes (Tulving et al., 1994b)

Activation in encoding-time tasks

Study of words, objects, faces > fixation control (Kelley et al., 1998)

Study of objects, words, nonsense words > noise patterns (Martin et al., 1997)

Study of varied > repeated single scene (Stern et al., 1996)

Words subsequently remembered > subsequently forgotten (Wagner et al., 1998)

Scenes subsequently remembered > subsequently forgotten (Brewer et al., 1998)

No activation despite retrieval success

No activation for memory vs gender judgments for faces (Sargent et al., 1992)

No activation for new vs old sentences (Tulving et al., 1994a)

formally in a strong positive correlation across subjects and conditions between test performance and medial temporal lobe activation.

Data supporting this account

The Nyberg et al. (1996) study provides the findings most directly supportive of the retrieval success account. Some further support can be drawn from the Kapur et al. (1995) PET study. As noted in the previous section, this study found greater hippocampal system activation in conditions in which subjects were to distinguish repeated from novel nonfamous faces, or identify which famous faces were of politicians, compared to a condition in which they were to identify the gender of each face. The two conditions that showed hippocampal activation thus were those in which performance required subjects to successfully retrieve stored information about (the identity or the prior occurrence of) a face, as distinguished from the condition in which they just needed to make a perceptual judgment about a face.

Data not handled by this account

We see four classes of findings that would seem to present problems for the retrieval success idea (see Table 2). The first class of findings involves studies in which differential hippocampal system activation is observed across conditions that all entail successful retrieval. This is exemplified by a PET study by Maguire et al. (1997), in which London taxicab drivers were asked to do four "recall" tasks: (1) recall a route from one place to another in the familiar city of London, (2) recall the location of a famous landmark to which they had never been, (3) recall the plot of a familiar movie, and (4) recall a particular scene from a familiar movie. Greater (right) hippocampal system activation was seen during recall of routes than during any other condition, even though successful performance in *any* of the conditions required successful retrieval of information, and the performance levels were shown to be comparable across conditions. There is no explanation within the retrieval success account for the variance in hippocampal activation observed across these conditions.

A second class of findings that cause problems for the retrieval success idea concerns studies in which there is no hippocampal system activation in conditions where there is successful retrieval. Two illustrative examples are PET studies by Sargent et al. (1992) and Tulving et al. (1994a). The Sargent et al. procedure was very similar to the Kapur et al. (1995) study cited above as support for the retrieval success account. Subjects were shown a set of faces and objects (some of which were repeated) and were asked either to recognize/identify the repeated objects/faces or indicate the gender of the face. Despite the fact that successful performance on the recognition/identification tasks required successful retrieval of previously stored memory, no hippocampal system activation was observed here. The Tulving et al. (1994a) study is the one, mentioned above, in which no hippocampal system activation was observed for previously presented vs. novel sentences. One must be careful not to make too much of these failures to see hippocampal activation since these are studies in which *no*

was said by a male or female speaker (perceptual encoding); for the other list they had to decide whether each word referred to a living or non-living thing (semantic encoding). Subjects were subsequently tested for recognition memory while being scanned, in a series of test blocks that assessed memory separately for perceptually encoded and semantically encoded words. Greater (left) medial temporal lobe activation was observed for blocks that tested words from the semantically encoded list compared to the perceptually encoded list. The fact that here, as elsewhere, there was a higher rate of successful recall of semantically encoded words compared to perceptually encoded words suggested to Nyberg et al. (1996) that increased hippocampal activation for semantically encoded words was a consequence of the role of this region in successful recall, i.e., in successfully gaining access to some memory representation. This connection was seen more

condition produces hippocampal activation, an outcome that could be caused by a number of different factors, as we noted earlier.

The next class of findings would seem to present a serious challenge to the retrieval success idea. These are studies in which hippocampal system activation is observed for new items and may even be greater for new items than for previously studied items. Successful reactivation of previously stored memory must be greater for materials that were actually studied previously than for novel materials. Yet, the imaging findings used to support the novelty account in the previous section, such as the Tulving et al. (1994b) study, show exactly the opposite pattern—more hippocampal activation for novel materials—and thus necessarily go against the retrieval success account. The retrieval success idea and the novelty idea (and the data that might support one vs. the other) are in direct conflict, and hence neither one will be able to accommodate the full range of imaging data.

A similar conclusion emerges from the final class of findings. These involve encoding-time studies, in which hippocampal system activation was observed during study or passive viewing conditions. Stern et al. (1996) found hippocampal system activation bilaterally when subjects studied color scenes in an fMRI study. Martin et al. (1997) found hippocampal system activation when subjects viewed nameable objects, words, or nonsense words in a PET study. In Kelley et al.'s (1998) fMRI study, hippocampal system activation was observed when subjects actively or passively encoded words, nonfamous faces, or line drawings of objects. Unless it is argued that encoding, and even passive viewing, of all of these various kinds of stimuli involves successful reactivation of previously stored memory and that this reactivation is what is driving the hippocampal activity observed at encoding time, such results represent a serious problem for the retrieval success account of hippocampal function. Note that in these studies hippocampal activation was seen for nonsense words (Martin et al., 1997) and for unfamiliar faces (Kelley et al., 1998), neither of which are likely to have any prior representations stored in memory. Furthermore, two recent studies used single-trial event-related fMRI methods to show that hippocampal activation observed during encoding of words (Wagner et al., 1998) or of scenes (Brewer et al., 1998) predicted subsequent memory test performance; i.e., that memory test performance is related on a trial-by-trial basis to operations performed at encoding time rather than at retrieval. Hippocampal activity in encoding-time studies would seem to be in line with a novelty account in that novel items would likely elicit more encoding time operations than would repeated items, suggesting again that the novelty and retrieval success ideas are in direct conflict, with neither capable of handling the full range of imaging data.

Contact with neuropsychological and other findings?

Although the retrieval success idea fared poorly in accounting for the full range of imaging data, we should take a moment before leaving this section to consider the extent to which it does or does not make contact with the neuropsychological literature. There

was much discussion in the 1970s and 1980s about whether amnesia was fundamentally a deficit—and hence whether the hippocampal system played a critical role—in retrieval processes, encoding processes, or storage and/or consolidation processes. Although Warrington and Weiskrantz (1968, 1970) staked out an early position in support of a retrieval deficit hypothesis of amnesia, we believe that the currently prevailing views are either agnostic about which is the critical stage of processing or else have a hybrid theory of hippocampal involvement that cuts across the stages of processing. Certainly there is no compelling evidence from neuropsychological work suggesting that the hippocampal system is uniquely involved in retrieval processes.

Stage of memory processing rather than domain of memory processing?

We have noted that neither the retrieval success account nor the novelty account is capable of accommodating the full range of imaging data on the role of the hippocampal system in memory. Rather than just dismissing these two accounts, however, it might be more useful to generalize these two ideas somewhat, treating them as being more generally about the role of the hippocampal system in two different stages of memory processing: encoding and retrieval. In that case, the question being addressed by these accounts concerns the *stage* of memory processing rather than the *domain* of memory processing in which the hippocampal system is involved. Recent discussions in the literature suggest that various portions of the hippocampal system may be involved differentially in these two stages of memory processing, as was noted earlier. This issue is raised in several papers in this volume. In the current paper, however, we stick to the issue of what domain of processing is handled by the hippocampal system, as addressed in each of the following three accounts.

Explicit (Vs. Implicit) Memory

Account of hippocampal function

Unlike the two proposed accounts just discussed, this idea about hippocampal function comes from outside the domain of functional imaging. Based on performance dissociations in normal subjects and amnesic patients, Graf and Schacter (1985) proposed the distinction between explicit and implicit memory. Explicit memory is said to involve conscious recollection of some prior study episode, whereas implicit memory permits the effects of previous experience to be manifested without requiring gaining conscious access to any specific experience. It is proposed that the hippocampal system plays a critical role in explicit memory.

Initial application to imaging

The first application of this account to functional imaging appeared in a PET study by Squire et al. (1992). Subjects studied word lists outside of the scanner. Their memory was subsequently tested in a number of different conditions while being scanned. At test they were given word stems and asked to complete the stems either: with the first word that comes to mind (priming condition), with a word from the study list (memory condition), or

TABLE 3.

Explicit Memory Account of Hippocampal Function**Account of hippocampal function**

Plays critical role in explicit memory

Initial application to imagingCued recall > completion [or baseline] of word stems
(Squire et al., 1992)**Best case for account**Recognition > object judgments (Schacter et al., 1995,
1997)**Other data in favor**Recall of VR "places" > viewing of scrambled versions
(Aguirre & D'Esposito, 1997)**But**Activation in encoding-time tasksStudy of words, objects, or faces > fixation control
(Kelley et al., 1998)Study of objects, words, or nonsense words > noise control
(Martin et al., 1997)Study of varied vs repeated single scenes (Stern et al.,
1996)Differences in activation across conditions that all involve
explicit rememberingExplicit remembering of new > old scenes in (Tulving et
al., 1994b)Retrieval of routes > landmarks, movie plots, movie
scenes (Maguire et al., 1997)No activation for explicit vs implicit memory comparisonNo activation for cued recall vs completion of word
stems (Buckner et al., 1995)No activation for recall vs generate or repeat category-
exemplar pairs (Shallice et al., 1994)

with the first word that comes to mind that was *not* on the study list (baseline condition). In the memory and priming conditions, the stems were constructed such that half could be completed to words from the study list. Hippocampal system activation was found bilaterally for the memory condition, which involved explicit memory instructions, as compared to either the priming condition, which involved implicit memory instructions, or the baseline condition. Hippocampal activation was also found for the priming-baseline comparison. The finding that hippocampal activation was greatest under explicit memory instructions supports the explicit memory account. Squire et al. (1992) also attributed the hippocampal activation seen for the priming-baseline comparison to subjects gradually switching to an explicit memory strategy even in the priming condition, when they began to realize that the word stems in this condition could be completed from the words they had previously studied.

Data supporting this account

Perhaps the strongest data we can offer in support of the explicit memory account of hippocampal function comes from the

Schacter et al. (1995, 1997) PET studies in which subjects studied possible and impossible objects and were tested in the scanner while making either possible/impossible object decisions or (explicit) recognition memory judgments. Hippocampal system activation was observed when subjects made (explicit) recognition judgments for either new or studied possible or impossible objects. Hippocampal activation was greatest for recognition of studied possible objects compared to new possible objects, consistent with when explicit remembering would be most needed. No hippocampal activation was found in the studied impossible-new impossible object comparison, presumably because subjects have no representations of impossible objects to explicitly remember. And no hippocampal activation was observed when making possible/impossible judgments about the possible objects, presumably because explicit remembering of previous exposures to real objects is not necessary in order to determine that a given object is indeed possible.

Other support can be drawn from Aguirre and D'Esposito (1997), in which subjects were given training in navigating around in a virtual reality (VR) environment containing 16 distinct places or landmarks with distinct names. Subjects were then scanned while they viewed various VR places, name-place pairings, or scrambled versions of places and names. In different conditions they matched landmarks and names, or identified the direction required to move between two places, or pushed buttons arbitrarily to scrambled place/name combinations (control condition). Hippocampal system activation was observed bilaterally for both conditions requiring explicit memory of the landmarks and names compared to the control condition involving scrambled displays.

Data not handled by this account

Three classes of findings would seem to present difficulties for the explicit memory account of hippocampal function (see Table 3). The first class concerns findings of hippocampal system activation in encoding-time tasks. As was discussed earlier, hippocampal system activation has been observed during encoding of words (Martin et al., 1997; Kelley et al., 1998; Wagner et al., 1998), objects (Kelley et al., 1998; Martin et al., 1998), faces (Kelley et al., 1998), nonsense words (Martin et al., 1997), or scenes (Stern et al., 1996; Brewer et al., 1998). Yet, at encoding time, particularly in the passive viewing conditions included in some of these studies, there is not likely to be much, if any, explicit remembering of specific prior learning episodes. The explicit memory account is fundamentally a retrieval-time theory (although not the same as the retrieval *success* idea), concerned with a particular kind of remembering. Accordingly, this account will necessarily be consistent only with the retrieval-time data and in conflict with the encoding-time data.

The second class of findings that seems problematic involves studies showing differences in hippocampal activation across conditions that all involve explicit remembering. One example of this would be the Tulving et al. (1994b) finding of greater hippocampal activation for explicit remembering of new scenes versus old scenes. It is difficult to understand why novel scenes, for

which there are not previously stored representations, would elicit greater explicit remembering than would previously studied scenes. As per our discussion above, this could well be an encoding effect, with novel material eliciting more elaborate or better encoding than what is elicited by repeating materials. As such, this experiment may just be another example of the difficulties that the explicit memory account has with encoding-time data. However, an example more clearly related to retrieval-time processing is from the Maguire et al. (1997) study of London taxicab drivers. As we saw earlier, greater hippocampal system activation was obtained during recall of routes than during any of the other three recall conditions (famous landmarks, movie scenes, or movie plots), even though successful performance in *any* of the conditions required explicit remembering. Unless one wanted to argue that the explicit remembering demand differed across these various conditions (i.e., that for whatever reason more explicit remembering is entailed in recalling routes), the explicit memory account cannot explain the variance in hippocampal activation across the conditions.

The final class of findings we can cite entails no hippocampal activation for the critical explicit memory condition. Shallice et al. (1994) failed to find hippocampal system activation for recalling (i.e., explicitly remembering) category-exemplar pairs in their PET study. The Buckner et al. (1995) PET study, discussed earlier, failed to find hippocampal activation in any of their series of experiments on cued recall vs. completion of word stems, despite using the same methods as in Squire et al. (1992), the study that had provided the original application of the explicit memory account to functional imaging. It is entirely possible that subjects in the latter study were using explicit remembering in both experimental and control conditions, regardless of instructions, and thus failed to show (differential) hippocampal activation because this system was active in *both* conditions. Alternatively, these failures to detect the expected hippocampal activation could be due to statistical or technical limitations rather than an actual absence of activation, as we have discussed in considering the other accounts, and hence does not provide that powerful an argument against the explicit memory account by itself. But taken together with the other two classes of findings that go against the predictions of the explicit memory account, we can see that the explicit memory account fails to handle the full range of imaging data.

Contact with neuropsychological and other findings?

The explicit memory account was intended to capture phenomena of normal memory and amnesia and hence is well grounded in the neuropsychological literature. The distinction between explicit and implicit memory has been widely used to describe aspects of impaired vs. spared performance in amnesia. Accordingly, the shortcomings we pointed to, above, in the ability of the explicit memory account of hippocampal function to handle the full range of current imaging data would seem to be disappointing, suggesting what seems to be a lack of concordance between the findings from neuropsychological and imaging studies. This seems particu-

larly true when one considers that the bulk of the early functional imaging studies (e.g., Shallice et al. 1994; Buckner et al., 1995), which found the hippocampal system to be such a recalcitrant target, were designed specifically with the explicit-implicit memory distinction in mind. However, current research on amnesia also points to shortcomings of the explicit-implicit memory distinction, suggesting that here too it fails to account for the full range of data. Research showing impaired vocabulary learning in amnesia, even when tested with implicit memory methods, and impaired memory for the relations among objects in scenes in amnesia, even when tested with eye movement monitoring methods that assess memory implicitly, calls into question a characterization of hippocampal function in terms of explicit memory (see Cohen, 1997). Accordingly, we will continue our search here for an account that will accommodate more nearly the full range of functional imaging data and that will also conform with the data from other converging methods.

Spatial (Cognitive) Mapping

Account of hippocampal function

As championed by O'Keefe and Nadel (1978), this view holds that the hippocampal system is fundamentally designed to construct, maintain, and make use of spatial maps of the environment. It derives its primary support from the very compelling findings of hippocampal neurons with place fields (discussed in a previous section, above) and of profound spatial learning and memory deficits in rats with hippocampal system lesions.

Initial application to imaging

This view of hippocampal function was first and, thus far, most successfully applied to functional imaging studies in the report by Maguire et al. (1997), in which they used PET to image the hippocampal system of experienced London taxi drivers as they retrieved information about routes (i.e., engaged in route finding) around London. As we have already discussed, greater activation of (right) hippocampal system structures was seen during recall of route information than during recall of famous landmarks, movie plot lines, or movie scenes.

Data supporting this account

Other support can be derived from the Aguirre and D'Esposito (1997) PET study in which subjects learned to navigate around in a virtual reality environment. Subjects were then scanned while they made judgments about the appearance or relative position of particular places in the VR environment compared to a control condition involving scrambled versions of the same stimuli. Hippocampal system activation was observed bilaterally for both conditions that tested memory of the learned VR places compared to the control condition. One further study we can cite in support of the spatial idea is one by Owen et al. (1996), who looked at memory for objects and locations while subjects encoded, then retrieved, information about a set of familiar objects presented in various locations on a screen. Assessing separately memory for

TABLE 4.

Spatial Mapping Account of Hippocampal Function**Account of hippocampal function**

Is a spatial memory [cognitive mapping] system

Initial application to imaging

Generating/recalling routes through city > recalling landmarks, movie scenes, or movie plots (Maguire et al., 1997)

Best case for account

Generating/recalling routes through city > recalling landmarks, movie scenes, or movie plots (Maguire et al., 1997)

Other data in favor

Recall of VR "places" > viewing of scrambled versions (Aguirre & D'Esposito, 1997)

Retrieving location > object information (Owen et al., 1996)

But

No activation in hippocampus even in clearly spatial tasks

During recall of VR "places" vs viewing of scrambled versions (Aguirre & D'Esposito, 1997)

For retrieving location vs object information (Owen et al., 1996)

Activation in tasks that are not predominantly about spatial processing

Encoding of words, faces, line drawings > fixation control (Kelley et al., 1998)

Encoding of line drawings, words, nonsense words > noise patterns (Martin et al., 1997)

Encoding of varied > repeated single scenes (Stern et al., 1996)

Hc activation differs across conditions that are equally [non]spatial

New > old scenes (Tulving et al., 1994b)

Varied > repeated single scenes (Stern et al., 1996)

Studied > new possible objects (Schacter et al., 1995, 1997)

Memory > gender judgments for faces (Kapur et al., 1995)

object identity and location, greater (right) hippocampal system activation was seen when tested on locations than when tested on object identity.

Data not handled by this account

There are three sets of findings that would seem to provide problems for the spatial mapping account of hippocampal function (see Table 4). The first set of findings relate to something that may be more of a quibble than a major challenge to the spatial view. In both the Aguirre and D'Esposito (1997) and Owen et al. (1996) studies cited above in support of the spatial account of hippocampal function, no activation was found in the hippocam-

pus itself; both of these studies noted that their activations were from parahippocampal cortex. We have already discussed the fact that failure to see the expected activation in the expected brain region may arise for various reasons, and also the fact that it may be easier to obtain findings from the parahippocampal region than from hippocampus itself for purely technical reasons (although the above findings involved PET, where some of the potential problems that make finding activation in hippocampus in MR imaging difficult do not apply). But the spatial account has made clear that the hippocampus itself should be the focal point of spatial (cognitive) mapping ability, and the neurons with the best place fields in rats are in hippocampus proper. Perhaps further studies will help to clarify the localization of relevant functional activity related to spatial processing in the hippocampal system.

A second set of findings seems to cause significant difficulty for the spatial account. These involve studies in which hippocampal system activation is produced in a variety of tasks that have little or nothing to do with spatial mapping as defined in the spatial theory of hippocampal function. This is illustrated well by the large number of studies showing hippocampal activation for encoding (even during passive viewing) of single words (Martin et al., 1997; Kelley et al., 1998; Wagner et al., 1998), objects (Kelley et al., 1998; Martin et al., 1998), letter strings (Martin et al., 1997), faces (Kelley et al., 1998), or scenes (Stern et al., 1996; Brewer et al., 1998), in which it is difficult to see how the basic processing entailed would depend in any significant way upon spatial mapping processes.

A third set of findings that seems to be a poor fit for the spatial account involves studies in which differential hippocampal activation is seen across conditions that are equally (non)spatial, i.e., where the spatial view cannot account for the variance in the results across conditions. We'll note a few examples from studies we've already discussed above. Tulving et al. (1994b) reported greater hippocampal activation for novel than for repeated scenes; Stern et al. (1996) found more hippocampal activation for a set of different scenes than for one scene presented repeatedly; Schacter et al.'s (1995, 1997) studies indicated greater activation in the hippocampal system for previously studied rather than new possible objects; and Kapur et al. (1995) reported more hippocampal activation when making memory judgments rather than gender judgments to faces. In all these cases, the stimuli were identical across conditions that elicited more or less activation of hippocampal system structures, and it is difficult to see how their dependence on spatial mapping processes differed in any way. Taken together, it is clear that the spatial view cannot account for the full range of findings from functional imaging.

Contact with neuropsychological and other findings?

The fact that the range of tasks that produce hippocampal system activation can be seen to extend beyond the domain of spatial mapping brings the imaging data into correspondence with neuropsychological and neurophysiological findings. The memory impairment of amnesic patients clearly extends beyond spatial deficits, as we saw in our discussion about the globalness of

impairment in amnesia, just as it does in both rodent and primate models of amnesia (see Squire, 1992; Cohen and Eichenbaum, 1993; Eichenbaum et al., 1994; Zola-Morgan, 1997). Likewise, the firing properties of hippocampal neurons extend beyond space, permitting the hippocampal system to encode a variety of conjunctions or relations among the elements of the environment (see Eichenbaum, 1996; Eichenbaum and Cohen, 1988).

Relational Memory Processing (Declarative [Vs. Procedural] Memory)

Account of hippocampal function

Extending the declarative-procedural memory distinction, originally offered by Cohen and Squire (Cohen and Squire, 1980; Cohen 1984; Squire, 1987, 1992) to account for the pattern of impaired vs. spared memory abilities in amnesia, Cohen and Eichenbaum proposed that the hippocampal system is critically involved in memory binding or relational memory processing. This system binds together converging inputs from various processors, permitting it to mediate representations of the relationships among various objects and events (Cohen and Eichenbaum, 1993; Eichenbaum et al., 1994). It does this binding in an automatic and obligatory way, a point to which we will return below.

Initial application to imaging

This idea was first tested in the neuroimaging literature by Cohen et al. (1994) in an fMRI study in which subjects were presented with stimuli composed of faces, names, and icons, and were either to study and recognize the previously presented face-name-icon triplets from among re-pairings of the same stimuli, or were to make gender discriminations. We found greater hippocampal activation for learning and remembering the triplets than for making gender judgments on the same stimuli (see Cohen et al., 1997, for further discussion of these results).

Data supporting this account

Perhaps the strongest support for the relational memory account from the functional imaging work comes from a PET study by Henke et al. (1997). In that experiment, subjects were shown a series of pictures of a person and of a house (either the interior or the exterior) simultaneously. The task instructions either required subjects to decide if the person was an inhabitant or a visitor to the house, and thus encouraged them to make an association between (i.e., bind) the person and the house, or to make separate decisions about the person (is it male or female?) and the house (is it an exterior or interior view?), thus encouraging them to encode the house and person separately. Henke et al. (1997) found greater (right) hippocampal system activation when the materials were encoded relationally than when they were encoded separately, supporting the claim that the hippocampal system is involved in memory binding.

TABLE 5.

Relational Memory Account of Hippocampal Function

Account of hippocampal function

Mediates [automatic & obligatory] binding of relations among perceptually distinct elements of scenes or events

Initial application to imaging

Binding faces-names-icons > gender decisions (Cohen et al., 1994)

Best case for account

Encoding face-house relationships > making judgments about face and houses separately (Henke et al., 1997)

Other data in favor

Study of varied > repeated single scenes (Stern et al., 1996)

Recognition > object judgments (Schacter et al., 1995, 1997)

Explicit remembering of new > old scenes (Tulving et al., 1994b)

Associative > perceptual encoding of scenes (Montaldi et al., 1998)

Memory > gender judgments for faces (Kapur et al., 1995)

Generating/recalling routes through city > recalling landmarks, movie scenes, or movie plots (Maguire et al., 1997)

Semantically > perceptually encoded words; correlation between retrieval and activation (Nyberg et al., 1996)

But

Differences in relational demands across conditions, but no

Hc activation

No activation for recall vs generate or repeat category-exemplar pairs (Shallice et al., 1994)

No activation for recall of word stems vs baseline (Buckner et al., 1995)

In assessing which other imaging findings might support this account, it seemed that each of the various studies that earlier were considered the best data in support of the other accounts also provided clear support for the relational memory idea. Consider first the Tulving et al. (1994b) and Stern et al. (1996) studies cited in support of the novelty account, in which greater hippocampal activation was found for novel scenes than for previously viewed scenes. More encoding and relational binding of the various elements in these scenes would be expected for never-seen vs. already-seen items, and hence greater hippocampal activation would be predicted by the relational account. This would be expected to be particularly evident in the Stern et al. (1996) study, in which the experimental condition entailed presenting a brand new scene every 3 seconds whereas the control condition had the same single scene presented every 3 seconds. The experimental condition would necessarily invoke more relational processing of

the many new relationships appearing within and across the constantly changing scenes, than would be the case for the control condition with the single unchanging scene. More generally, an effect of stimulus novelty on hippocampal activation makes good sense within the relational account of hippocampal function. Interestingly, in attempting to explain why they observed hippocampal activation in their task at a time, several years ago, when many other imaging studies (most of them using verbal stimuli) had been less successful, Stern et al. (1996) stated: "The key difference between imaging studies that do or do not show the hippocampal activity is probably not specifically related to the use of verbal versus visual information, but more likely relates to the complexity and relational characteristics of the information being presented. Simple verbal stimuli, unlike complex visual pictures and faces, do not require the formation of new representations or relationships."

We would concur completely; we would just add that our relational account (and our declarative-procedural theory, more generally) explains *why* this should be so: When conditions differ sufficiently in the amount of relational memory processing or memory binding that they encourage or require, then significant differences will be observed in the amount of hippocampal activation elicited.

Turning to the various encoding-time data discussed above, the success of these studies in eliciting greater hippocampal activation in experimental conditions involving a series of changing scenes, faces, words, etc., compared to control conditions that presented subjects with just a fixation point (e.g., Kelley et al., 1998; Wagner et al., 1998; Brewer et al., 1998) or noise patterns (e.g., Martin et al., 1997) seems to provide good support for the relational memory account. These control conditions place absolutely minimal demands on a relational memory or memory binding system of the kind we have proposed, which makes it possible to generate experimental conditions capable of eliciting much more relational memory processing and thereby permits hippocampal activation to be observed.

Indeed, this was a prediction from our relational memory theory, which prompted us to participate in the Kelley et al. (1998) study that found hippocampal activation during (even passive) encoding of words, objects, and nonfamous faces. In further work with the same nonfamous faces, plus famous faces, we have found hippocampal activation for faces compared to noise patterns made by drastically rearranging the pixels of those faces (Ryan et al., 1998). Another way to think about these encoding-time findings within the relational memory account is this: The hippocampal system provides the critical machinery for binding together the various elements encountered in our interaction with the environment; and it does binding automatically and obligatorily, in the sense that no strategic intervention is necessary (though it certainly can be influential). Whenever presented with a series of varied stimuli, the hippocampal system will be actively engaged in relational memory processing and hippocampal activation will be detectable. By contrast, when there are no objects or just very few objects as input to the system, as when the stimuli consist of just a fixation cross or noise patterns, there is little or no

binding that can be done; the hippocampal system will be less active and will show little or no activation in functional imaging studies.

The studies cited in support of the retrieval success account, such as Kapur et al. (1995) and Nyberg et al. (1996), would seem to provide equally strong support for the relational account. Kapur et al. (1995) found greater hippocampal system activation in conditions in which performance required subjects to successfully retrieve stored information about the identity or the prior occurrence of a face, as distinguished from conditions in which they just needed to make a perceptual judgment about a face to determine gender. In other words, when subjects needed to process the relation between the presented face and information stored in memory— be it episodic information (or explicit memory) about the previous exposure to that face during the experiment, or episodic and semantic information about the occupation/identity of the person depicted in the photo— more hippocampal activation was seen. Nyberg et al. (1996) reported more hippocampal system activation for words that had been encoded semantically than for words encoded perceptually. Good semantic encoding, involving relating the item to its various semantic associates, would certainly invoke the relational memory processing we attribute to the hippocampal system and thus would be expected to produce greater hippocampal activation. A similar view can be offered of the recent event-related fMRI findings (Wagner et al., 1998; Brewer et al., 1998) tying hippocampal activation at encoding to subsequent successful memory performance on a trial-by-trial basis. Among the operations most likely to more fully engage the hippocampal system and lead to better remembering are relational memory processes. An excellent example of this connection comes from the Montaldi et al. (1998) study, in which greater hippocampal activation was seen when subjects performed associative encoding of scenes than when they performed perceptual encoding of the same scenes.

The hippocampal system activation observed in the Schacter et al. (1995, 1997) studies, cited as providing strong support for the explicit memory account, provides just as strong support for the relational memory account. The recognition judgment task is a relational memory task in which subjects must attempt to relate the object presented with a previously established representation made at the time of encoding. More generally, it is the relational nature of all explicit memory tasks (the requirement of making contact with some specific study episode related to the test item) that causes hippocampal system damage to impair explicit memory test performance (see Cohen and Eichenbaum, 1993; Cohen et al., 1997) and that causes explicit memory tests to have a chance of activating the hippocampal system.

Finally, the data cited as providing strong support for the spatial mapping account would also provide good support for the relational account and help to illustrate an important point about the relational account. Maguire et al. (1997) found greater hippocampal activation for recalling routes than for recalling landmarks, film plots, or film frames. All these conditions involve relational processing, but they differ considerably in the amount

and nature of relational processing required. As intentionally designed by Maguire et al. (1997), route recall involved both topographical and sequential relations; film plot recall depended largely on sequential relations and landmark recall depended just on topographical relations; and film frame recall depended neither on topographical or sequential relations. On their own analysis of these different tasks conditions, one can see that route recall requires the greatest amount of relational processing, and thus would be expected to produce the most hippocampal activation. This is exactly the result they obtained. More generally, the kinds of spatial processing that are required for navigating successfully through the environment and that would be seen by the likes of O'Keefe and Nadel as spatial mapping functions can instead be seen as a subset of relational memory processing. Finding hippocampal activation in conditions that invoke the processing of spatial relations, therefore, would provide support for both accounts equally. However, findings such as those considered earlier, in which hippocampal activation is observed in conditions invoking *non*spatial relational processing supports only the relational account.

Data not handled by this account

We cannot claim to have examined every single functional imaging study in the world's literature in preparing this review; for example, we may well be unaware of some recent findings reported in other articles in this volume. However, to our knowledge, the only imaging data that are not well handled by this account come from studies in which no hippocampal activation was observed despite conditions that would seem to invoke relational memory processing. Two examples, from studies we've already discussed here, are the reports by Shallice et al. (1994) and Buckner et al. (1995), involving word stems and category-exemplar pairs. As noted several times already, however, this is the weakest form of negative evidence, requiring the use of a null result, which may reflect technical or statistical limitations rather than an absence of the activation, to dispute a theory. One possible methodological issue in any imaging study concerns picking a set of conditions that differ sufficiently in the degree to which the cognitive process under study is invoked. In the case of relational memory processing, we believe that it is always engaged to some extent whenever there are stimulus objects that can be bound together. Hence, the selection of experimental conditions is particularly crucial here and, as suggested by Stern et al. (1996), it may be difficult to invoke enough relational memory when using verbal materials to see any differential hippocampal activation. One solution to this, that seems to work, is to pick a control condition that pushes the relational memory demand as close as possible to zero, for example, as suggested above, by using non-objects as the stimuli.

In contrast to all of the other accounts we have considered in this review, there are no examples of findings, of which we are aware, in which hippocampal activation occurred in the *wrong* conditions. Rather, as far as we can determine, the pattern of hippocampal findings reported in all of the neuroimaging studies

examined in this review are in line with the predictions of this account and can provide support for it.

Contact with neuropsychological and other findings?

The declarative-procedural memory theory (Cohen and Squire, 1980; Cohen, 1984; Squire, 1987, 1992) was intended to capture phenomena of normal memory and amnesia; it is well grounded in the neuropsychological literature. The more recent elaboration of the theory into the current relational memory account, i.e., that the role of the hippocampal system is in binding together multiple streams of information, regardless of whether memory is tested explicitly or implicitly (see Cohen and Eichenbaum, 1993; Eichenbaum et al., 1994; Cohen et al., 1997) permits this framework to accommodate a huge body of findings in the human and animal literatures, including both neuropsychological and neurophysiological data. The conclusion of the current review, that the relational memory account can accommodate more nearly the full range of imaging data than any other explanatory account suggests that the findings and interpretations of the imaging work might now be in correspondence with the findings and interpretations of the other lines of cognitive neuroscience work in suggesting a critical role for the hippocampal system in declarative memory and relational binding.

CONCLUSIONS

We have reviewed the rapidly expanding literature on imaging of memory and the hippocampal system, and have evaluated the fit of a large set of data to a set of possible explanatory accounts of hippocampal function. With the caveats that (1) we may not have analyzed all imaging studies in the existing literature, (2) we have not evaluated the fit of the imaging data to all possible theories of hippocampal function, limiting ourselves here to five of the most promising or visible proposals, and (3) we have taken all the data at face value, giving them equal weight, without attempting to reject certain studies on methodological, statistical, or other grounds, we have reached several conclusions: First, there is enough systematicity to the imaging data to entertain a unified account. Second, there seems to be good correspondence between the imaging data and neuropsychological data. And, third, the relational memory account can accommodate more nearly the full range of imaging data than any other explanatory account of hippocampal function.

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