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The Medial Temporal Lobe and Recognition Memory

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Abstract

The ability to recognize a previously experienced stimulus is supported by two processes: recollection of the stimulus in the context of other information associated with the experience, and a sense of familiarity with the features of the stimulus. Although familiarity and recollection are functionally distinct, there is considerable debate about how these kinds of memory are supported by regions in the medial temporal lobes (MTL). Here, we review evidence for the distinction between recollection and familiarity and then consider the evidence regarding the neural mechanisms of these processes. Evidence from neuropsychological, neuroimaging, and neurophysiological studies of humans, monkeys, and rats indicates that different subregions of the MTL make distinct contributions to recollection and familiarity. The data suggest that the hippocampus is critical for recollection but not familiarity. The parahippocampal cortex also contributes to recollection, possibly via the representation and retrieval of contextual (especially spatial) information, whereas perirhinal cortex contributes to and is necessary for familiarity-based recognition. The findings are consistent with an anatomically guided hypothesis about the functional organization of the MTL and suggest mechanisms by which the anatomical components of the MTL interact to support of the phenomenology of recollection and familiarity.

Keywords

recollection; familiarity; hippocampus; perirhinal cortex; parahippocampal cortex; entorhinal cortex; amnesia

INTRODUCTION

Imagine an occasion when you are walking across campus and see someone who seems vaguely familiar. When she greets you, you are quite sure you know this person, and yet you can not recall when you met her or why you know her. A casual conversation ensues and you search for clues with innocuous questions. Further embarrassment is avoided when she says something about a meeting last week. Suddenly you recall her name, where the meeting was, and some of the topics discussed there.

This common scenario illustrates the two kinds of subjective experiences that occur during recognition. One is a sense of familiarity, which is experienced rapidly and varies from a weak intuition to a compellingly strong belief. The other experience is recollection, which involves the recovery of qualitative associations prompted by a critical cue. Beyond the distinction in subjective experiences, considerable evidence now demonstrates that familiarity and recollection are two different forms of memory, which exhibit very different functional characteristics (see Yonelinas 2002). It remains unclear, however, whether recollection and familiarity are supported by distinct brain processes or instead emerge from a single neural mechanism. In particular, scholars debate how these kinds of memory are supported by regions

in the medial temporal lobes (MTL). Here, we begin with an overview of the behavioral and event-related potential studies indicating that recollection and familiarity are distinct and then focus on studies that shed light on the neural mechanisms of recognition. Guided by the neuroanatomy of the MTL, we review studies of recognition memory in humans with amnesia following MTL lesions and results from functional imaging studies in healthy subjects. We also consider animal models that have been used to identify brain areas that are critical to aspects of recognition memory and to characterize neuronal activity related to recognition performance.

Medial temporal lobe (MTL)

the combination of the parahippocampal region and hippocampus

Methodological limitations are associated with any particular approach. For example, it is often difficult to ascertain the precise locus and extent of damage in amnesic patients, and conflicting results in these studies are often attributed to the possibility of damage outside the medial temporal region. Functional imaging studies of humans can be used to localize neural correlates of recognition processes, but these methods do not test whether a given region is truly necessary for these processes. Animal models provide precise anatomical localization of lesions and recording sites, but it can be difficult to map concepts from psychological studies of humans onto the kinds of tasks used in animal models. Given that any research method has unique strengths and limitations, our approach is to seek convergence across different methods. Evidence from these different approaches is indeed converging on an anatomically based model in which different medial temporal areas implement distinct information processing functions in the service of recollection and familiarity.

RECOLLECTION AND FAMILIARITY

Studies of human memory have indicated that recollection and familiarity reflect two functionally distinct memory processes. Although evidence for this distinction comes from a variety of different experimental paradigms (see Table 1), here we focus on three methods (i.e., response time, receiver operating characteristics, and event-related potential studies) that have been particularly important in motivating this distinction and in providing insight into the nature of these processes (for reviews see Diana et al. 2006, Rugg & Yonelinas 2003, Yonelinas 2002).

As illustrated in the opening vignette, familiarity typically becomes available more quickly than does recollection. For example, forcing subjects to make speeded recognition responses has only a small effect on recognition tests in which subjects are required only to discriminate between studied and nonstudied items. However, it leads to robust reductions in performance on relational recognition tests (sometimes called associative, source, or context recognition tests) that require the retrieval of specific information about each item, such as where or when it was studied (e.g., Gronlund et al. 1997, Hintzman & Caulton 1997, Yonelinas & Jacoby 1994). In some recognition experiments, familiarity and recollection processes are placed in opposition by requiring participants to reject items that are highly familiar (e.g., either items that were studied on a particular list or foil items that are highly similar to studied items). As the amount of time allowed to make a recognition response is increased, the probability of incorrectly accepting these highly familiar items first increases then decreases (e.g., Doshier 1984, Gronlund & Ratcliff 1989, Hintzman & Curran 1994, McElree et al. 1999). The increasing, then decreasing nature of these functions indicates that at least two temporally distinct processes or memory components are operating in recognition memory: a rapidly available familiarity process that leads to incorrect responses when fast responses are required, and a

slower recollective process that allows subjects to reject those items when participants are given more time.

A second line of evidence indicating that recognition involves two distinct memory processes comes from the analysis of recognition memory receiver operating characteristics (ROCs). ROCs are examined typically by collecting recognition confidence responses then plotting hits against false alarms as a function of confidence. As illustrated in Figure 1, ROCs observed in item-recognition tests are curvilinear when plotted in probability space and approximately linear when plotted in z-space. The z-space transformation allows for a relatively simple way of quantifying the nature of the functions and testing various recognition theories. Figure 1a shows that increasing study time leads the ROCs to increase in sensitivity (the height or “bowing” of the probability curve and an increase in the intercept in z-space) but to retain the same degree of ROC asymmetry in the probability curve (constant slope in z-space; for reviews, see Ratcliff et al. 1994, A. Yonelinas & C. Parks, submitted). In contrast, conditions where the meaning of items (“deep” encoding), compared with conditions where the perceptual features of items (“shallow” encoding), are emphasized during study (Figure 1b), increase overall performance but lead the ROC to become more asymmetrical (i.e., an increase in z-intercept and a decrease in z-slope; for reviews see Glanzer et al. 1999, A. Yonelinas & C. Parks, submitted). The dissociation between sensitivity and asymmetry indicates the existence of two or more functionally independent memory processes or components.

Another important finding was that ROCs in relational-recognition tests tend to be much flatter than item recognition ROCs, and z-transformed ROCs (z-ROCs) exhibit a pronounced U-shape (see Figure 1c). U-shaped z-ROCs are seen almost always in relational-recognition tests including both source memory (e.g., Glanzer et al. 2004, Hilford et al. 2002, Slotnick et al. 2000, Yonelinas 1999) and associative memory (Healy et al. 2005, Kelley & Wixted 2001, Rotello et al. 2000, Yonelinas et al. 1999). The “U” shape is predicted if recollection contributes to high-confidence recognition responses (Yonelinas 1994). This finding rules out other pure familiarity-based signal-detection models that predict that z-ROCs should always be linear (e.g., the unequal variance signal-detection model).

The processes that determine the shape of the recognition ROC are likely the same as those underlying subjective reports of recollection and familiarity, as well as the ability to retrieve relational information. That is, the ROC observed in item-recognition tasks can be quantified by fitting a nonlinear function to the observed data to derive estimates of recollection and familiarity (Yonelinas 1994, 2001a). In brief, the y-intercept provides a measure of recollection (i.e., the proportion of old items that are recollected), and the degree of curvilinearity in the ROC provides a measure of familiarity (i.e., the difference in familiarity strength between old and new items). The reasoning behind these interpretations is that recollection supports high-confidence recognition responses, whereas familiarity increases gradually across a wide range of recognition confidence. There are two additional methods commonly used to estimate recollection and familiarity. One method involves requiring that subjects distinguish items they “remember” using qualitative information about the study event versus items they merely “know” were studied on the basis of familiarity in the absence of recollection (Yonelinas & Jacoby 1995). The other method involves a process-dissociation procedure in which one measures recollection as the ability to retrieve where or when an item was studied, and familiarity as the ability to recognize an item given that it was not recollected (Jacoby 1991). The convergence of results across these various measurement methods attests to the construct validity of the recollection/familiarity distinction and suggests that recollection and familiarity can be indexed using either the ROC, remember/know, or relational-recognition methods.

Receiver operating characteristic (ROC)

Comparison of the proportion of hits to false alarms under varying confidence levels or response biases

Hit

correct recognition of an experienced item

False alarm

incorrect identification of a new item as old

ERP

event-related potential

Recordings of event-related brain potentials (ERPs) during memory tasks have provided further evidence to support the distinction between recollection and familiarity (for reviews see Friedman & Johnson 2000, Rugg & Yonelinas 2003). Numerous studies have reported temporally, topographically, and functionally distinct ERP correlates of recollection and familiarity during retrieval (for evidence of encoding differences see also Yovel & Paller 2005). For example, Figure 2 illustrates two distinct ERP modulations commonly observed during recognition: a mid-frontal negativity onsetting ~400 ms after stimulus onset that is associated with familiarity, and a parietally distributed positivity beginning ~500 ms after stimulus onset that is associated with recollection. The parietal effect is evident for correct, but not incorrect, relational-recognition judgments (e.g., Curran 2004), for remember-but-not-know responses (Curran 2004, Duarte et al. 2006, Duzel et al. 1997, Smith 1993), and with the most confidently recognized items (Woodruff et al. 2006). The mid-frontal effect is also related to successful recognition, but it tends to increase gradually with increases in recognition confidence (Woodruff et al. 2006). It also does not differentiate between recognized, recollected items and recognized, nonrecollected items. The earlier onset of the familiarity effects is in good agreement with the behavioral results indicating that familiarity is available earlier than recollection. The finding that recollection and familiarity are related to ERP modulations that exhibit distinct scalp topographies suggests that these processes are associated with activity in distinct neural generators.

Implications of the Behavioral and ERP Data

The behavioral data reviewed above indicate that recollection and familiarity have qualitatively different characteristics during both the encoding of new information into memory and the retrieval of previously encoded information (see Table 1; for reviews see Diana et al. 2006, Yonelinas 2002). These studies indicate that there is a broad set of measurement tools that can be used to measure recollection and familiarity and that can thus be used to help identify the neural underpinnings of these processes. Moreover, the finding that the ERP correlates of recollection and familiarity are qualitatively different provides preliminary evidence that these processes depend on partially distinct brain regions.

ANATOMICAL ORGANIZATION OF THE MEDIAL TEMPORAL LOBE MEMORY SYSTEM

At least 50 years of evidence has established the importance of structures within the MTL as critical to memory. Anatomical studies have identified the major subregions of the MTL in

humans, monkeys, and rodents (Figure 3, *top*) and have suggested a hypothetical functional organization for memory processing (Figure 3; for reviews see Burwell 2000, Witter et al. 1989).

At the broadest level, the MTL can be subdivided into the perirhinal cortex, the parahippocampal cortex, and entorhinal cortex (collectively referred to as the parahippocampal region), and the hippocampus (including the dentate gyrus, Ammon's horn, and subiculum). Most of the neocortical input to the perirhinal cortex comes from association areas that process unimodal sensory information about qualities of objects (i.e., “what” information), whereas most of the neocortical input to the parahippocampal cortex (called postrhinal cortex in rodents) comes from areas that process polymodal spatial (“where”) information. Subsequently, the “what” and “where” streams of processing remain largely segregated as the perirhinal cortex projects primarily to the lateral entorhinal area, whereas the parahippocampal cortex projects mainly to the medial entorhinal area. Some connections exist between the perirhinal and parahippocampal cortices and between the entorhinal areas, but the “what” and “where” information converge mainly within the hippocampus. The cortical outputs of hippocampal processing involve feedback connections from the hippocampus successively back to the entorhinal cortex, then perirhinal and parahippocampal cortices, and finally, neocortical areas from which the inputs to the MTL originated.

Implications of the Anatomical Data

This anatomical evidence suggests the following hypothesis about how information is encoded and retrieved during memory processing. During encoding, representations of distinct items (e.g., people, objects, events) are formed in the perirhinal cortex and lateral entorhinal area. These representations along with back projections to the “what” pathways of the neocortex can then support subsequent judgments of familiarity. In addition, during encoding, item information is combined with contextual (“where”) representations that are formed in the parahippocampal cortex and medial entorhinal area, and the hippocampus associates items and their context (as first proposed by Mishkin et al. 1983). When an item is subsequently presented as a memory cue, the hippocampus completes the full pattern and mediates a recovery of the contextual representation in the parahippocampal cortex and medial entorhinal area. Hippocampal processing may also recover specific item associates of the cue and reactivate those representations in the perirhinal cortex and lateral entorhinal area. The recovery of context and item associations constitutes the experience of recollection. In the succeeding sections, we consider the evidence on the functional roles of these brain areas in support of this hypothesis.

Parahippocampal region

a set of cortical areas surrounding the hippocampus, including the perirhinal cortex, parahippocampal cortex (called postrhinal cortex in rodents), and entorhinal cortex

RECOGNITION MEMORY AND AMNESIA

Studies of recognition memory in amnesia have been driven by two major classes of theories: those that posit a single process that supports recognition and those that posit two distinct underlying processes.

One-Process Theories

One of the earliest views stated that the MTL is critical for recollection, whereas association cortex supports familiarity (e.g., Huppert & Piercy 1978, Mayes et al. 1985, Wickelgren 1979). According to this view, patients with MTL damage should exhibit recollection deficits,

whereas familiarity-based recognition should remain unaffected. An alternative one-process theory argues that the MTL is equally important for both recollection and familiarity (Squire 1994, Squire & Zola 1998). By this view, MTL damage should lead to equivalent deficits in recollection and familiarity.

Neither of these theories provides an adequate account of MTL amnesia. For example, several studies have shown that MTL patients can discriminate between old and new items relatively well, but they are profoundly impaired at discriminating between recently and frequently presented items (e.g., Huppert & Piercy 1978, Mayes et al. 1989, Meudell et al. 1985). These results indicate that recollection is more impaired than familiarity in MTL patients, which is inconsistent with the claim that the MTL is equally important for both processes. Even when item recognition is matched, MTL patients typically perform poorly in relational-recognition tests that require them to remember when or where an item was presented (see Yonelinas 2002 for review). Studies using ROC and other estimation methods have verified that recollection was more impaired than familiarity, but in addition they have indicated that familiarity was also disrupted in MTL patients relative to controls (see Yonelinas et al. 1998). This pattern of broad deficits in recollection and familiarity following MTL damage has been observed in studies using the remember/know procedure (e.g., Blaxton & Theodore 1997, Kishiyama et al. 2004, Knowlton & Squire 1995, Moscovitch & McAndrews 2002, Schacter et al. 1996), the process dissociation procedure (Verfaellie & Treadwell 1993), and the ROC procedure (Yonelinas et al. 1998). These results are inconsistent with theories that assume that the MTL supports recollection but plays no role in supporting familiarity.

MRI

magnetic resonance imaging

Hypoxia/ischemia

temporary loss of oxygen typically resulting in neuronal damage

Two-Process Theories

In 1994, Eichenbaum et al. proposed that two separate processes within the MTL contribute to recognition memory. They argued that the hippocampus is critical for recollecting associations of a memory cue, whereas the parahippocampal region can support recognition of familiar cues in isolation. According to this proposal, only one process is affected by selective hippocampal damage, leading to partial or complete sparing of performance based on the other process; the extent of sparing and appearance of the deficit on any given task would depend on task parameters that favor one or the other process. Brown & Aggleton (2001) extended this distinction, suggesting that the hippocampus is critical for episodic recollection, whereas the perirhinal cortex supports judgments about the recency and familiarity of specific stimuli.

Both of these models predict that hippocampal damage should disrupt recollection but not familiarity, whereas damage to the surrounding parahippocampal region should lead to deficits in familiarity. These models can account for the typical pattern of severely impaired recollection and mildly deficient familiarity in MTL patients. That is, disproportionate recollection deficits are expected if the damage disproportionately affected the hippocampus as compared with the parahippocampal region. However, the strongest prediction of these models is that patients with selective hippocampal damage should exhibit a selective impairment in recollection.

More recent research has tested these theories by attempting to dissociate recollection and familiarity in patients with selective hippocampal damage. Typically, these patients developed memory loss following transient cerebral hypoxia. The hippocampus is particularly vulnerable to hypoxic-ischemic damage, and postmortem studies as well as structural imaging studies have demonstrated that mild hypoxia results in neuronal loss confined largely to the hippocampus (e.g., Gadian et al. 2000, Hopkins et al. 1995, Zola-Morgan et al. 1986). An important caveat about these studies is that it is impossible to rule out damage to regions outside the hippocampus, particularly in cases in which the hypoxic event is severe. Notably, structural magnetic resonance imaging (MRI) scans can fail to reveal neuronal loss that is apparent in histological examinations (Rempel-Clower et al. 1996).

Several studies have reported that hypoxic patients exhibit disproportional deficits in relational compared with item recognition (Giovanello et al. 2003b, Holdstock et al. 2005, Mayes et al. 2002, Turriziani et al. 2004). In some cases, the relational-recognition deficit appears to be reduced when the paired items are from the same category (e.g., face pairs compared with word-face pairs; Vargha-Khadem et al. 1997), but not in others (Turriziani et al. 2004). Studies using estimation methods have largely confirmed that recollection can be selectively impaired in hypoxic patients. For example, one study (Yonelinas et al., 2002) examining ROCs showed that mildly hypoxic patients exhibited severe deficits in recollection but demonstrated normal familiarity (Figure 4*a,b*). The results were verified by using remember/know measures in the same patients (Figure 4*c*). Moreover, the covariation between recall, recognition, and hypoxic severity (as indexed by coma duration) was examined using structural equation modeling methods in a large sample of hypoxic patients and indicated that hypoxic severity predicted the degree to which recollection, but not familiarity, was impaired (Figure 4*d*). A similar pattern of deficient recollection and preserved familiarity was reported in a patient with relatively selective hippocampal atrophy related to meningitis (Aggleton et al. 2005).

However, some studies of severely impaired hypoxic patients have failed to find selective recollection deficits following limited hippocampal damage. For example, Cipolotti et al. (2006) found that a severely hypoxic patient exhibited deficits in recollection and familiarity indexed using the ROC procedure. However, in addition to hippocampal atrophy, the patient also exhibited parahippocampal region atrophy, which might have led to the familiarity deficits. Global impairments in item and relational recognition, and in familiarity and recollection, have also been observed in a group of amnesic patients with diverse etiologies (Wais et al. 2006, Gold et al. 2006, Manns et al. 2003, Stark & Squire 2003). In the absence of histological evidence, however, it is possible that the familiarity deficits observed in this group were also due to damage outside the hippocampus (Yonelinas et al. 2004).

Although human studies of amnesia have been useful in differentiating the role of the hippocampus from the surrounding parahippocampal gyrus, they have provided only limited evidence regarding the differential roles of the perirhinal and parahippocampal cortex in recognition memory because both regions are typically damaged together in MTL patients. Nonetheless, some evidence indicates that the parahippocampal cortex may be important particularly for the recall of spatial information (e.g., Bohbot et al. 2000).

Implications of the Findings on Amnesia

Extensive MTL damage leads to deficits in recollection and smaller but consistent deficits in familiarity. These results indicate the MTL is not a unified memory system that is critical only for recollection (Mayes et al. 1985) or that it is equally important for recollection and familiarity (Squire 1994). The results are more consistent with models stating that recollection is dependent on the hippocampus, whereas familiarity can be supported by the surrounding parahippocampal region (Brown & Aggleton 2001, Eichenbaum et al. 1994). Studies on

amnesic patients have not provided definitive information on putative functional distinctions between the perirhinal and parahippocampal cortical areas.

FUNCTIONAL IMAGING OF RECOLLECTION AND FAMILIARITY

Functional imaging studies have linked activity throughout the MTL to successful recognition performance (see Henson 2005), but these studies have led to some confusion regarding the precise roles of different MTL subregions in recognition memory. For example, many studies have contrasted MTL activity during retrieval tests between studied (“old”) items and items that were not previously studied (“new”). Activation differences between old and new items could be related to increased recollection and/or familiarity elicited by old items (Rugg & Yonelinas 2003), increased encoding of new items (Stark & Okado 2003), or possibly nondeclarative memory processes such as repetition priming (Grill-Spector et al. 2006). Other studies have contrasted activation during encoding of items that were subsequently remembered against items that were subsequently forgotten (e.g., Brewer et al. 1998). In these contrasts, activations could reflect the formation of representations that support recollection, familiarity, or both processes. Accordingly, differentiating MTL activity associated with recollection and familiarity requires contrasts that more specifically isolate these processes.

Neuroimaging studies typically identify neural correlates of recollection by contrasting activity between recollected items and recognized items that were not recollected. For example, some studies use a remember/know test (Tulving 1985) and then contrast activity between items that elicited “remember” responses (presumably using recollection) and items that elicited “know” responses (presumably using high familiarity in the absence of recollection). Another approach is to use relational-recognition tests and then contrast activation between recognized items that were associated with successful retrieval of contextual information against recognized items for which the participant could not retrieve the specific contextual association.

Neural correlates of familiarity are typically examined by contrasting activation elicited during processing of nonrecollected items that generated varying levels of familiarity strength. As described above, most imaging studies have identified neural correlates of familiarity by contrasting activity between items that were recognized and not recollected (i.e., items eliciting a “know” response or items that were recognized but associated with incorrect source/relational judgments) against items that were not recognized (i.e., “misses”). Another potentially more powerful method capitalizes on the fact that familiarity varies in a continuous manner as a function of response confidence (see Recollection and Familiarity). A number of studies (Daselaar et al. 2006, Montaldi et al. 2006, Ranganath et al. 2003, Yonelinas et al. 2005) have used graded confidence ratings to identify regions where encoding- or retrieval-related activity increases or decreases monotonically with recognition confidence.

For several reasons, one might expect some variability in findings among studies. First, it is unlikely that any given imaging contrast will be 100% process-pure. Thus, a “recollection” contrast might also index some activity related to familiarity. Also, structures within the MTL are in close proximity, near the resolution of current functional MRI methodology, and these structures are highly interconnected. Thus, neural processing that originates in one region can be expected to activate closely connected neighboring regions, resulting in more extensive MRI signal changes (see Logothetis & Wandell 2004). For these reasons, we considered the overall pattern of findings in the imaging literature and asked whether activity in different MTL subregions tends to be correlated with recollection and/or familiarity (Table 2).

Finally, although anatomical studies in nonhuman primates and rats suggest an important functional distinction between lateral and medial areas of the entorhinal cortex, these areas have not yet been differentiated in humans. Given our current understanding of these regions (3), we consider signal in the anterior parahippocampal gyrus to reflect mainly activation of

the perirhinal and lateral entorhinal areas and signal in the posterior parahippocampal region to reflect mainly activation of the parahippocampal cortex with or without medial entorhinal area activation.

Activation in the Hippocampus and Posterior Parahippocampal Gyrus

Table 2 summarizes results from studies that have identified neural correlates of items, recollection of item-item associations, and/or familiarity in the MTL. Of the 19 contrasts that identified activation related to recollection, 16 (84%) reported hippocampal activation and 11 reported posterior parahippocampal activation (58%). A similar pattern was seen in the 6 contrasts related to recollection of associations: all 6 reported hippocampal activation (100%) and 3 (50%) reported posterior parahippocampal activation. Of the 15 contrasts that identified neural correlates of familiarity-based recognition, only 4 (27%) revealed hippocampal activation and 4 (27%) revealed posterior parahippocampal activation. In two of the studies reporting hippocampal activation correlated with familiarity (Daselaar et al. 2006, Yonelinas et al. 2005), the analyses included responses to old and new items. Given that old items typically receive high confidence ratings and new items receive low ratings, the hippocampal activations may have reflected encoding of new item-context associations (e.g., Stark & Okado 2003) rather than familiarity.

Overall, the results suggest that hippocampal activation during both encoding and retrieval is consistently higher for recollected than nonrecollected items and is generally insensitive to changes in familiarity strength. This pattern of results was consistent across different measurement techniques and different stimulus materials. A similar pattern of results, although not as consistent, is apparent in the posterior parahippocampal gyrus.

Activation in the Anterior Parahippocampal Gyrus

Table 2 reveals a very different pattern of results in the anterior parahippocampal gyrus. Only 2 of 19 (11%) contrasts related to item recollection reported activation in the anterior parahippocampal gyrus, whereas 13 of the 15 (87%) familiarity contrasts reported anterior parahippocampal activation. Anterior parahippocampal activation was reported in 4 of the 6 contrasts (67%) related to recollection of item-item associations. Thus, anterior parahippocampal activation is generally correlated with familiarity and rarely correlated with item recollection.

The relationship between anterior parahippocampal activation and familiarity differs between encoding and retrieval: Activation during encoding is higher for items that were subsequently rated as highly familiar than for items that were subsequently forgotten (Davachi et al. 2003, Kensinger & Schacter 2006, Kirwan & Stark 2004, Ranganath et al. 2003, Uncapher & Rugg 2005), whereas during retrieval, activation is lower for items that were highly familiar than for items that were forgotten (Daselaar et al. 2006, Gonsalves et al. 2005, Montaldi et al. 2006, Weis et al. 2004a). Results from studies using confidence ratings have progressed further by showing that activation during encoding increases monotonically with subsequent confidence ratings (Ranganath et al. 2003), whereas activity during recognition decreases monotonically with recognition confidence (Daselaar et al. 2006, Montaldi et al. 2006). Although this pattern might seem counterintuitive, it is strikingly consistent with results from imaging and physiological studies of rodents and monkeys that are reviewed below (see also Brozinsky et al. 2005, Henson et al. 2003).

As shown in Table 2c, anterior parahippocampal activation was sometimes (4 of 6 contrasts; 67%) correlated with recollection in studies that required participants to learn associations between two items, such as faces and names (Kirwan & Stark 2004), faces and words (Fenker et al. 2005), pictures and words (Eldridge et al. 2005), or pairs of unrelated words (Jackson &

Schacter 2004). These findings suggest that, at least under some conditions, the perirhinal cortex may support memory for associations between items, consistent with findings from studies on rats (Bunsey & Eichenbaum 1993) and monkeys (Murray et al. 1993).

Implications of the Imaging Data

Findings from the imaging literature are inconsistent with the idea that all MTL subregions contribute to an equivalent degree to recollection and familiarity-based recognition. Most compelling in support of this conclusion are within-study dissociations (e.g., Figure 5) in which anterior parahippocampal activation was selectively associated with familiarity and activity in the hippocampus and posterior parahippocampal gyrus was selectively associated with recollection (Daselaar et al. 2006, Davachi et al. 2003, Kensinger & Corkin 2004, Ranganath et al. 2003, Uncapher & Rugg 2005, Weis et al. 2004b). The findings are also inconsistent with a simple distinction between the hippocampus and the parahippocampal region. Instead, the results summarized above suggest a functional dissociation between the perirhinal cortex, where activation changes are consistently associated with familiarity, and the hippocampus and parahippocampal cortex, where activation changes are consistently associated with recollection. The results are similar across studies that examined subsequent memory effects at encoding and studies that examined activity during retrieval and across studies that used very different techniques to measure familiarity and recollection.

The findings from the imaging literature, along with the anatomical characteristics of the MTL (Figure 3), suggest that the hippocampus, the perirhinal cortex, and the parahippocampal cortex may each form unique representations that support recognition memory. In perirhinal cortex, encoding an item may elicit increases in the selectivity or efficiency (i.e., “strength”) of item representations. Consequently, during retrieval, increased familiarity is manifest as reduced activation of these representations (Brown & Aggleton 2001, Eichenbaum et al. 1994, Yonelinas 2002). In contrast, the parahippocampal cortex may encode representations of the global context in which an item was encountered (Bar & Aminoff 2003, Davachi et al. 2003, Ranganath et al. 2003), and the hippocampus may represent item-context associations (Davachi et al. 2003, Ranganath et al. 2003). Activation of these representations during retrieval may support recollection.

ANIMAL MODELS OF RECOGNITION MEMORY

Animal models offer a substantial improvement in the resolution with which we can examine the effects of selective damage to particular MTL areas and allow us to identify the behavioral correlates of neural activation at the level of the units of information processing. These methods have been applied in recognition-memory models in which monkeys or rats are trained to respond differentially to new and previously experienced stimuli or in which we observe their natural tendency to explore novel stimuli.

Delayed Nonmatch to Sample (DNMS)

In the delayed nonmatch to sample (DNMS) paradigm an initially novel “sample” object is presented, and after a variable delay, the subject is rewarded for selecting another novel (i.e., nonmatching) object over the sample (Figure 6). Monkeys with extensive MTL lesions perform well if the delay is a few seconds, but recognition deteriorates rapidly at longer delays (Mishkin 1978). This effect is analogous to the rapid forgetting rate observed in amnesic patients (Squire et al. 1988). A similar severe and rapid decline in recognition is also observed after damage limited to the perirhinal cortex alone (Nemanic et al. 2004) (Figure 6) or in combination with parahippocampal or entorhinal cortex in monkeys (Meunier et al. 1993, Zola-Morgan et al. 1989) and in rats (Otto & Eichenbaum 1992a, reviewed in Brown & Aggleton 2001, Steckler et al. 1998).

Delayed nonmatch to sample (DNMS)

recognition test wherein the subject is rewarded for choosing a novel stimulus over a familiar one

Spontaneous novelty exploration

recognition test that exploits the tendency to preferentially investigate novel over previously experienced stimuli

In contrast, monkeys with selective damage to the hippocampus (Nemanic et al. 2004) (Figure 6) or entorhinal cortex (Buckmaster et al. 2004) can perform normally on DNMS even at substantial memory delays. In some studies, a small but statistically significant deficit was observed at a very long delay (Zola et al. 2000), but in other studies, no deficit was observed even at long memory delays or when animals were required to remember a long list of stimuli (Murray & Mishkin 1998). In rats, DNMS performance is also intact following selective hippocampal damage (see Mumby 2001 and Steckler et al. 1998 for detailed reviews), although some studies report partial impairment at long delay intervals or with very large lists of sample objects (Clark et al. 2001, Dudchenko et al. 2000, Steele & Rawlins 1993; reviewed in Mumby 2001).

Spontaneous Novelty Exploration

In studies that examine recognition by monitoring spontaneous exploration of familiar and novel stimuli, an object or picture is initially presented and then represented after a delay along with a novel stimulus (Figure 6). Animals typically spend approximately twice as much time investigating the novel stimulus over the previously experienced stimulus. Superficially, these paradigms seem to tap into the same recognition memory processes as does the DNMS task. However, there are differences in the nature of the stimuli and behavioral responses, as well as in the motivational basis for performance, that could influence the use of different memory strategies in the expression of recognition memory (Nemanic et al. 2004). Indeed, monkeys with selective hippocampal or parahippocampal cortex damage that show little or no deficit in DNMS have severe and rapidly apparent deficits on the spontaneous novelty exploration task (Figure 6) (Nemanic et al. 2004, Zola et al. 2000). In rats, some studies report no deficit (e.g., Mumby et al. 2002, Winters et al. 2004; reviewed in Mumby 2001) whereas other studies have observed impairment at long delays (Clark et al. 2000, Hammond et al. 2004), and observation of the deficit may depend on the amount of damage to the hippocampus (e.g., Broadbent et al. 2004). In contrast to the modest and variable deficit observed following damage to the hippocampus, ablation of the perirhinal cortex consistently results in a severe and rapidly developing deficit in monkeys (Nemanic et al. 2004) (Figure 6) and in rats (e.g., Ennaceur et al. 1996, Mumby et al. 2002, Norman & Eacott 2005, Winters et al. 2004, Winters & Bussey 2005).

In variants of recognition tasks during which rats must remember places, the hippocampus consistently plays an important role. Hippocampal damage causes severe and immediate deficits on DNMS tasks in which animals must remember arms of a recently visited maze (Olton et al. 1979) or complex visual cues that are composed as visually elaborated arms of a maze (e.g., Cassaday & Rawlins 1995; Prusky et al. 2004). In a variant of the spontaneous novelty exploration task where an initially presented object is moved to a new location or to a new environment during the test phase, selective hippocampal lesions consistently result in deficits even following relatively small lesions of the hippocampus that have no effect on exploration of novel objects (e.g., Eacott & Norman 2004, Mumby et al. 2002). Similarly,

damage to the parahippocampal cortex does not affect exploration of novel objects but results in severe impairment in recognizing objects after a change in position or context (Eacott and Norman 2004, Norman & Eacott 2005). These results suggest that the hippocampus and parahippocampal cortex may be involved particularly in memory for spatial scenes or context.

Resolving the Discrepancies: Two Components of Recognition Memory in Animals

One explanation for the partial and variable effects of hippocampal damage on object recognition memory is that the hippocampus supports only one of two processes that contribute to recognition performance (i.e., recollection), and the demand for this component varies across paradigms. This hypothesis was recently tested by training rats on a variant of DNMS in which they initially sampled a series of odors and then judged old and new test stimuli across a range of response criteria. These data were used to derive ROC functions, similar to the approach used in humans (See Recollection and Familiarity) (Fortin et al. 2004). Similar to the findings in healthy humans, the ROC curve of normal rats was asymmetrical and curvilinear, indicating both recollection and familiarity components of recognition (Figure 3*e, f*). By contrast, the ROC curve of rats with selective hippocampal damage was entirely symmetrical and identical to the familiarity component of the ROC of control animals, which indicated that recognition was supported primarily by familiarity. A strong recollection component was retained in normal rats when the memory delay was elongated to equate their overall accuracy with that of rats with hippocampal damage at the shorter delay. This observation indicates that deterioration of the recollection component of the ROC curve following hippocampal damage is not a consequence of a generally weakened memory but rather a selective loss of the contribution of recollection. The combined findings strongly support two-process over single-process models of recognition and identify the hippocampus as selectively critical to recollection. Furthermore, these findings explain the inconsistent effects of hippocampal damage on recognition memory in previous studies. In animals, as in humans, the presence and magnitude of deficits depend on the relative contributions of recollection and familiarity processes to each particular task.

Activity Patterns of Single Neurons in the Medial Temporal Region

During the performance of delayed matching and DNMS tasks, cells in the perirhinal and lateral entorhinal areas of monkeys and rats exhibit properties that suggest a role in recognition memory (reviewed in Brown & Xiang 1998, Desimone et al. 1995, Fuster 1995, Suzuki & Eichenbaum 2000). For example, many cells exhibit stimulus-specific responses that are enhanced or suppressed when the preferred stimulus is represented. Some of these neurons show diminished responses to stimulus repetition within a recognition memory trial but then recover their maximal responses; these cells could signal the recency of stimulus presentations. Other cells exhibit long-lasting decrements in responsiveness to stimuli, which could support recognition over extended periods. In most studies, more cells show suppressed rather than enhanced responses to stimulus repetition, and this mixture of responses has been attributed to a sharpening of the ensemble representation of items as a result of experience. Although stimulus-selective repetition effects are robust in perirhinal and lateral entorhinal area, they are not often observed in parahippocampal and medial entorhinal area. Instead, parahippocampal and medial entorhinal area neurons demonstrate strong spatial coding (Burwell & Hafeman 2003, Fyhn et al. 2004, Hargreaves et al. 2005), consistent with lesion studies demonstrating the importance of the parahippocampal cortex in recognition that relies on spatial context.

Hippocampal neurons in monkeys (Brown & Xiang 1998), rats (e.g., Otto & Eichenbaum 1992a), and humans (Rutishauser et al. 2006) do not show increased or decreased responses associated with repetition of specific stimuli during delayed matching and nonmatching tasks that test item recognition. Instead, hippocampal neurons show only general responses to

novelty or familiarity across a broad range of stimuli, suggesting a role in encoding the outcome of recognition experiences. In contrast with the absence of stimulus-specific responses in item-recognition tasks, results from studies of rats (e.g., Hampson et al. 1993; Moita et al. 2003; Wood et al. 1999, 2000), monkeys (e.g., Cahusac et al. 1993; Wirth et al. 2003), and humans (e.g., Ekstrom et al. 2003; Kreiman et al. 2000) suggest that hippocampal neurons encode associations between specific stimuli and a unique location or behavioral context. These results indicate that hippocampal firing patterns reflect unique conjunctions of stimuli with their significance, the animal's specific behaviors, and the places and contexts in which the stimuli occur (Eichenbaum 2004).

The observations from single neuron recordings have been confirmed by differential activation of the immediate early gene *fos* in neurons in the MTL (e.g., Wan et al. 1999). In these studies, rats are trained to view visual stimuli that are novel and familiar or familiar but spatially rearranged. *Fos* is activated by novel stimuli in the perirhinal and lateral entorhinal area but not in the hippocampus or postrhinal (parahippocampal) cortex. Conversely, *fos* is expressed in response to novel spatial arrangements of familiar stimuli, as well as in spatial learning (Vann et al. 2000), selectively in the hippocampus and postrhinal cortex but not in perirhinal cortex.

Implications of the Data from Animal Models

The convergence of findings from lesion and recording approaches in animals strongly supports the idea that different components of the MTL make distinct contributions to recognition memory. The combined findings on monkeys and rats suggest that perirhinal cortex lesions have a devastating effect on object-recognition memory. Conversely, the perirhinal cortex can support relatively intact recognition memory even when the hippocampus or neocortical input to the hippocampus is eliminated. Consistent with these findings, neurons in the perirhinal cortex encode and maintain representations of individual stimuli and signal their familiarity. In contrast, damage to the parahippocampal or medial entorhinal areas results in deficits in spatial recognition, and correspondingly, neurons in these areas encode spatial features of the environment and not individual stimuli.

Damage to or disconnection of the hippocampus has a relatively modest effect on item recognition but results in severe deficits in memory for spatial context and in the recollection component of item recognition. Correspondingly, hippocampal neurons encode configurations of items in the behavioral and spatial context in which they were experienced, a central feature of recollective memory.

CONCLUSIONS

The diverse lines of evidence reviewed above suggest that recollection and familiarity are functionally dissociable processes and that different MTL subregions make distinct contributions to recognition memory. Evidence from neuropsychological, neuroimaging, and neurophysiological studies of humans, monkeys, and rats indicates a specific role for the hippocampus in recollection and not familiarity. The parahippocampal cortex also contributes to recollection, possibly via the representation and retrieval of contextual (especially spatial) information, whereas perirhinal cortex contributes to and is necessary for familiarity-based recognition.

The findings are consistent with a novel, anatomically guided (Figure 3) hypothesis regarding the mechanisms by which different regions of the MTL may interact to support the phenomenology of recollection and familiarity: During encoding, information about stimuli to be remembered, processed by the perirhinal and lateral entorhinal areas, and information about their context, processed by parahippocampal and medial entorhinal areas, converge in the

hippocampus. When a previously encountered stimulus is processed, perirhinal and lateral entorhinal areas can signal its match to a preexisting item representation, observed as overall suppressed activation. This match signal can be propagated back to neocortical areas, which may be sufficient to generate the sense of familiarity without participation of the hippocampus. Additionally, processing of the stimulus may drive the recovery of object-context associations in the hippocampus that, via back projections, reactivate a representation of the contextual associations in the parahippocampal and medial entorhinal areas. These areas, in turn, project back to the neocortical areas that processed the context in which the item was previously encountered, thereby eliciting the subjective experience of recollection.

Our working hypothesis leads to several predictions, some of which have been tested in experiments described above or in other published studies, and some of which remain challenges for future experiments. One prediction is that the perirhinal and lateral entorhinal cortices encode individual items and thereby support familiarity-based recognition. Consistent with this prediction, damage to perirhinal cortex results in deficits in familiarity in human amnesic patients and severe impairment in item recognition in monkeys and rats across different recognition tests. Correspondingly, functional imaging studies in humans and single-neuron recording studies in monkeys and rats have revealed differential activation of the perirhinal cortex, as well as lateral entorhinal cortex in animals, when subjects view novel versus familiar stimuli. Furthermore, the pattern of decreased neural responses to familiar stimuli is similar across species and physiological measures and distinct from activation patterns associated with recollection (reviewed in Brown & Aggleton 2001, Brozinsky et al. 2005, Eichenbaum et al. 1994, Henson et al. 2003). One outstanding question is whether the human entorhinal cortex can be subdivided into functionally distinct lateral and medial areas similar to those described in animals.

Another expectation derived from the anatomical framework is that the parahippocampal and medial entorhinal cortices process spatial context and could play a more general contextual processing role. A paucity of evidence exists on this issue from studies of human patients. However, functional imaging studies have shown that the parahippocampal cortex is selectively activated when human subjects examine spatial scenes or objects that strongly evoke spatial as well as nonspatial contexts (Bar & Aminoff 2003) and during recollection of spatial or nonspatial contexts (Table 2*a,b*), whereas the perirhinal cortex is disproportionately activated during the object processing (Pihlajamaki et al. 2004). Converging results come from lesion studies in rats (Gaffan et al. 2004, Norman & Eacott 2005) and monkeys (Alvarado & Bachevalier 2005, Malkova & Mishkin 2003) have demonstrated that object-location recognition is impaired following damage to the parahippocampal cortex, whereas object recognition is impaired following perirhinal damage. Furthermore, results from single-unit recording studies and *fos* imaging indicate that neurons in rodent homologs of parahippocampal and medial entorhinal cortices show strong spatial coding, whereas perirhinal and lateral entorhinal neurons have poor spatial-coding capacities. In future studies it will be important to determine whether the parahippocampal region is generally activated during recollection or more specifically activated during retrieval of particular contextual information as a part of the recalled experience. Recollection of specific contextual information might be observed in imaging studies on human subjects as region-specific activations that match the kind of material retrieved and in single-neuron recording studies as reinstatement of specific firing patterns that match the retrieved contextual information. In addition, our hypothesis predicts that the perirhinal and lateral entorhinal cortices may be involved in recovery of specific item-item associations during recollection. Some evidence from the imaging (Table 2*b*) and single-neuron recording studies (Naya et al. 2001) is consistent with this prediction.

Our hypothesis also suggests that the hippocampus plays a specialized role in associating items and their contexts in the service of recollection. This claim is strongly supported by several

lines of evidence. Recent studies on human amnesic patients indicate that the hippocampus supports our ability to associate items in memory and to recollect contextual associations, as compared with recognition of single items based on familiarity. Parallel evidence from functional imaging studies strongly indicates that the hippocampus is selectively activated during item associations and contextual associations in support of recollection (Table 2; see also Addis et al. 2004, Davachi & Wagner 2002, Giovanello et al. 2003a, Prince et al. 2005). In animals, the hippocampus is selectively involved in the recollection component of recognition memory and recognition of spatial context. Correspondingly, hippocampal neurons are activated by stimuli in the spatial or temporal contexts in which they were experienced. These findings converge on the notion that the hippocampus supports recollective memory by associating items and their contexts. Future research can build on these findings by strengthening the connections between findings from animal models and the phenomenology of recollection in humans. A critical step toward this goal will be to determine whether the parameters that differentially influence recollection and familiarity in humans (see Table 1) have similar effects in animals in order to develop valid animal models that can support detailed analyses of information coding within subfields of the hippocampus.

Available evidence also suggests roles for the prefrontal cortex, parietal cortex, and diencephalon in familiarity and recollection (e.g., Aggleton & Brown 1999, Duarte et al. 2005, Kishiyama et al. 2005, Uncapher et al. 2006). A comprehensive understanding of the neurobiology of recognition will require a consideration of the contributions of these and other areas as they coordinate with the MTL. Although there remain many unanswered questions within the framework offered here, it provides a simple and testable working hypothesis about the functional organization of recognition memory by the MTL system.

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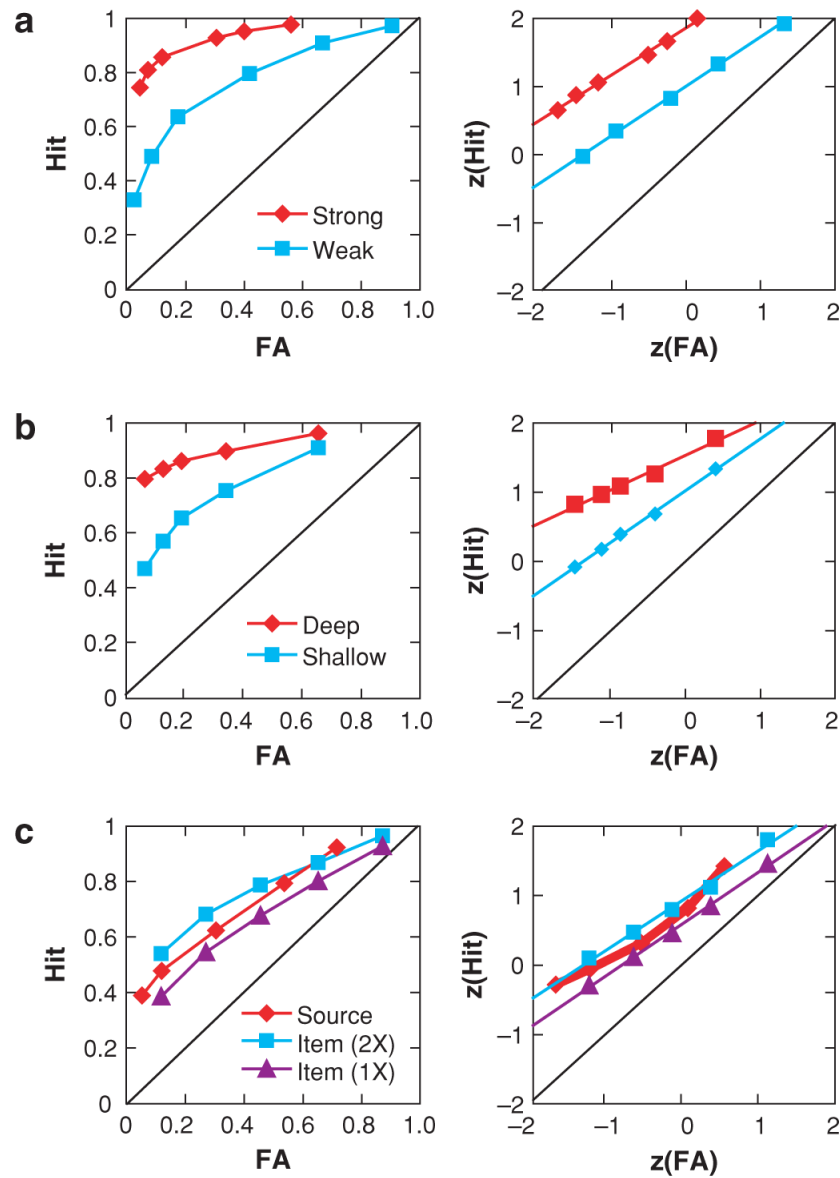


Figure 1. Receiver operating characteristic (ROC) analyses of recognition memory. Left panels plot probability of hits versus false alarms (FA). Right panels plot the same data normalized (z -Hit and z FA). Chance performance is represented by the diagonal in each panel. (a) ROCs for strongly encoded items (studied twice) and weakly encoded items (studied once) from Egan (1958, experiment 1). (b) ROCs for items studied under deep encoding conditions (i.e., rate the pleasantness of the word) and shallow encoding conditions (i.e., count the number of syllables in the word) (from Yonelinas et al. 1996). (c) ROCs in which subjects studied verbal items spoken once or twice by a male or female speaker. At test they were visually presented with the words and were to indicate how confident they were that the item had been presented earlier and whether it was presented by the male or female source (from Yonelinas 1997, experiment 3).

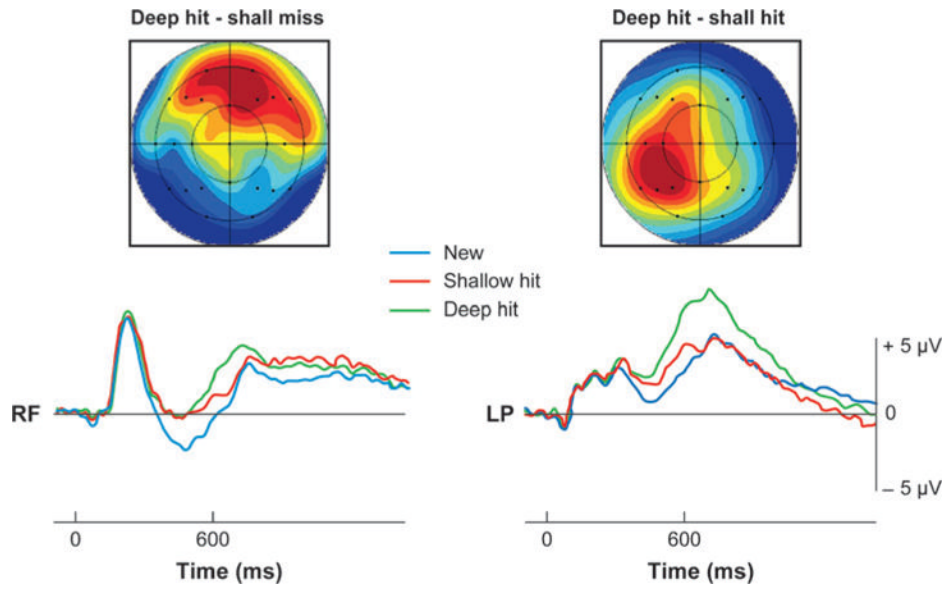


Figure 2. ERPs from Rugg et al. (2002) illustrating a mid-frontal ERP modulation (*left panel*) associated with familiarity and a parietally distributed (*right panel*) related to recollection. In this study, the familiarity effect was evident for deeply and shallowly encoding items, whereas the recollection effect was most pronounced for the deeply encoding items.

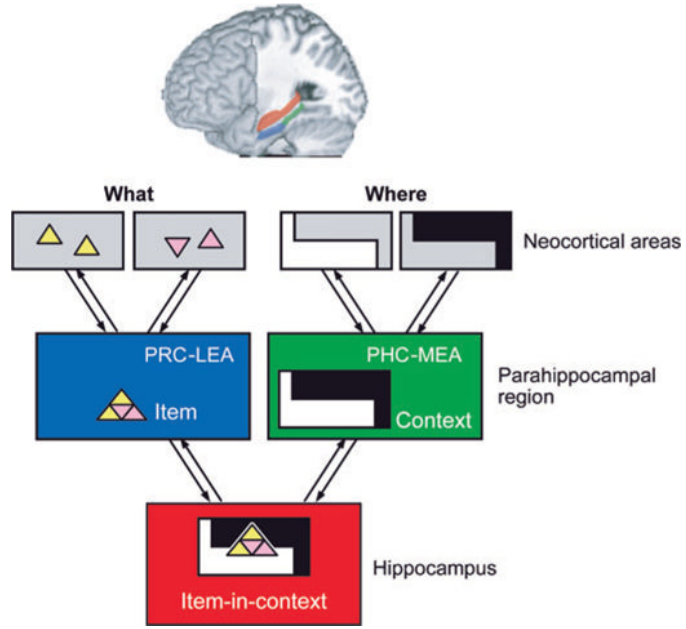


Figure 3. Functional organization of the MTL system. Neocortical input regarding the object features (“what”) converges in the perirhinal cortex (PRC) and lateral entorhinal area (LEA), whereas details about the location (“where”) of objects converge in the parahippocampal cortex (PHC) and medial entorhinal area (MEA). These streams converge in the hippocampus, which represents items in the context in which they were experienced. Reverse projections follow the same pathways back to the parahippocampal and neocortical regions. Back projections to the PHC-MEA may support recall or context, whereas back projections to the PHC-LEA may support recall of item associations.

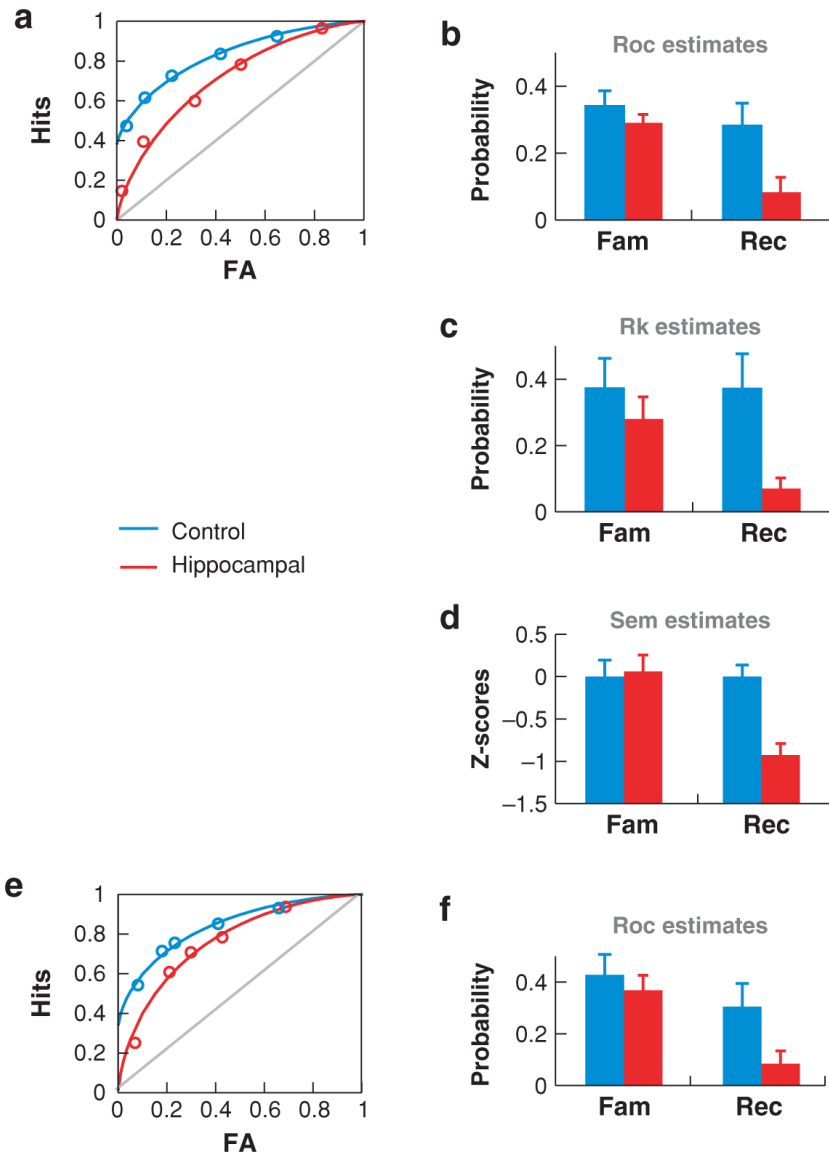


Figure 4.

Measures of recollection and familiarity in amnesic patients with expected hippocampal damage (Yonelinas et al. 2002) and in rats with selective hippocampal lesions (Fortin et al. 2004). (a) ROCs for the amnesic patients are lower and more symmetrical than those of the controls. (b) ROC measures of recollection (R) and familiarity (F) indicate that recollection, but not familiarity, is reduced in the amnesics (H) compared with controls (C). (c) R and F estimates derived from a separate remember/know experiment also indicate that recollection was disrupted in the amnesic patients whereas familiarity was unaffected. (d) R and F estimates derived using structural equation modeling (SEM) in a larger group of amnesic patients showed that increases in hypoxic severity led to a decrease in recollection but left familiarity unaffected. (e) ROCs for rats with hippocampal lesions are lower and more symmetrical than are those of control animals. (f) ROC measures indicated that familiarity is unaffected by hippocampal lesions.

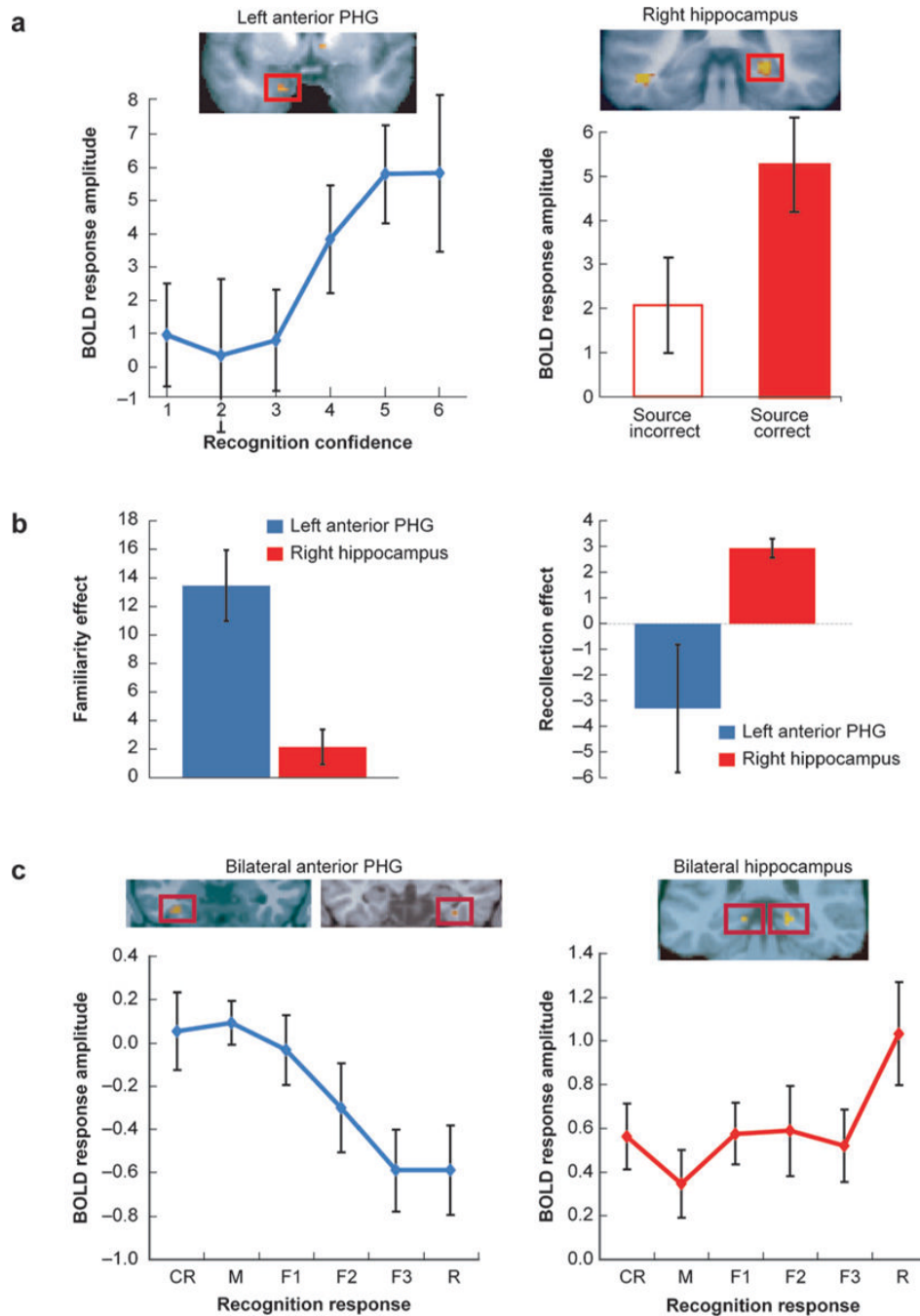


Figure 5. Double dissociations between hippocampal and anterior parahippocampal activity. (a) Data from Ranganath et al. (2003). Participants were scanned during encoding of words shown in red or green and subsequently were asked to rate their confidence regarding whether each word was shown in the scanner and to decide whether the word was shown in red or green during the study phase. Activity in the left anterior parahippocampal gyrus (PHG; *left*) during encoding was correlated with subsequent confidence ratings, suggesting a role in familiarity-based recognition. Encoding activity in the right hippocampus was correlated with accuracy on the relational-recognition test, suggesting a role in recollection. (b) Comparison of the magnitudes of subsequent familiarity (*left*) and recollection (*right*) effects in the left anterior PHG and right

hippocampal regions. The comparison revealed a reliable double dissociation between the two regions. (c) Data from Montaldi et al. (2006). Participants studied scenes and were scanned during recognition testing. For each item that was judged old, participants were to indicate if it was recollected (R) or to rate its familiarity on a 1–3 scale (F1–F3). Activation is separately plotted for correctly rejected new items (CR) and for old items that elicited new (M), F1–F3, and R responses. Activation in bilateral anterior parahippocampal regions (*left*) monotonically decreased with increasing confidence and did not differ between highly familiar items (F3) and items that were recollected. In contrast, activation in bilateral hippocampal regions (*right*) was increased specifically for recollected items, as compared with nonrecollected items, and was insensitive to gradations in familiarity strength.

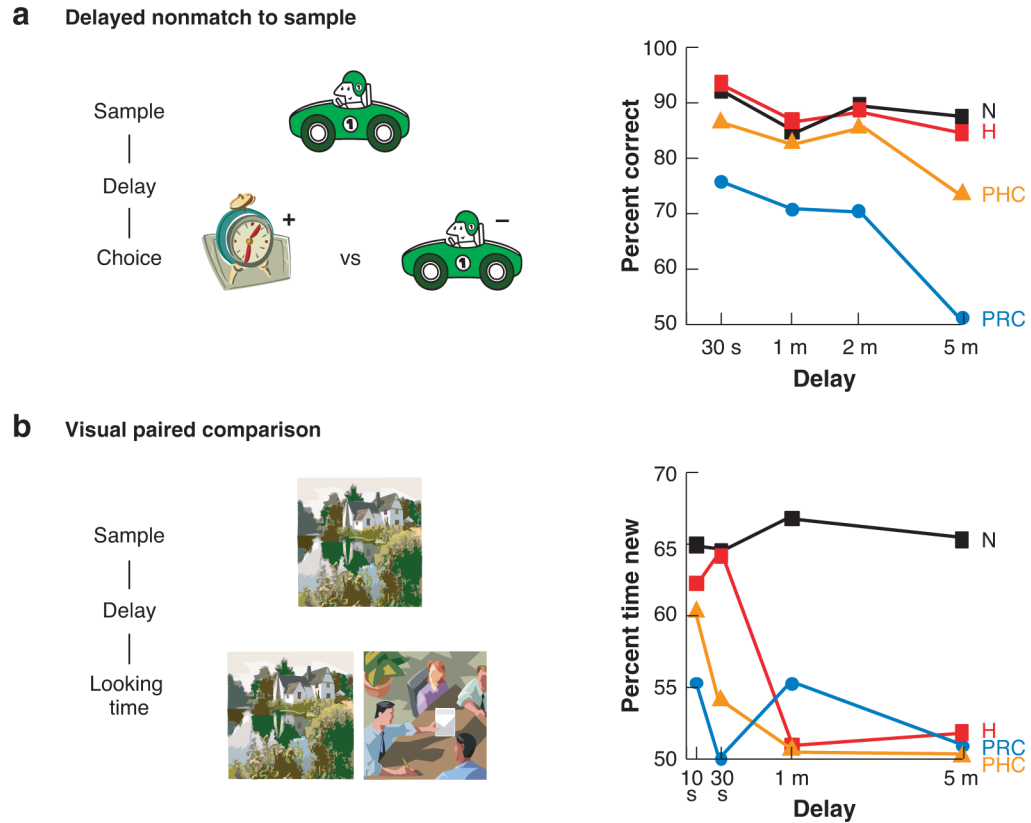


Figure 6. Performance of normal monkeys (N) and monkeys with lesions of the hippocampus (H), perirhinal cortex (PRC), or parahippocampal cortex (PHC) on two recognition memory tasks. (a) In the delayed nonmatch to sample task, animals must remember a sample object over a delay period, then select against it (nonmatch) in the choice phase. Normal monkeys show robust recognition over long memory delays, as do animals with hippocampal or PHC damage. PRC lesions result in rapid decay of memory. (b) In the visual paired comparison task, animals remember a once-viewed scene and later prefer to view a novel scene. Normal monkeys also show robust recognition over long delays in this task, but memory in animals with H, PHC, or PRC lesions rapidly decays (data from Nemanic et al. 2004).

Table 1

An overview of the functional characteristics of recollection and familiarity. The effects of encoding and retrieval manipulations on recollection and familiarity (for details see text and Yonelinas 2002). **, large effect; *, moderate effect; –, no effect

Manipulations	Recollection	Familiarity
Encoding		
Study time	**	**
Elaboration	**	*
Attention	**	*
Rote repetition	-	*
Retrieval		
Speeding	**	-
Attention	**	-
Fluency	-	**
Bias	-	**
Perceptual match (verb)	-	*
Brief delay	-	*
Long delay	**	**

Table 2
 MTL activation in studies that examined neural correlates of recollection and/or familiarity¹

Study	Method	Materials	Stage	Contrast	Hipp	PPHG	APHG
A. Recollection of items							
Davachi et al. 2003	SC/SI/Miss	words	En	SC > SI	b	1	none
Gold et al. 2006	SC/SI/Miss	words	En	SC > SI	none	none	1
Kensinger & Schacter 2006	SC/SI/Miss	emotional pictures	En	SC > SI	1	r	none
Kensinger & Schacter 2006	SC/SI/Miss	emotional words	En	SC > SI	1	none	none
Ranganath et al. 2003	SC/SI/1-6	words	En	SC > SI	r	r	none
Uncapher & Rugg 2005	RKN	words	En	R > K	1	none	none
Uncapher et al. 2006	SC/SI/Miss	words+2 sources	En	Both SC > 1 or 2 SI	r	none	none
Cansino et al. 2002	SC/SI/Miss	words	Re	SC > SI	r	1	none
Daselaar et al. 2006	1-6 conf	words	Re	6 > 1-5	1	none	none
Dolcos et al. 2005	RKN	neutral pictures	Re	R > K	b	r	none
Dolcos et al. 2005	RKN	emotional pictures	Re	R > K	b	b	none
Eldridge et al. 2000	RKN	words	Re	R > K	b	r	none
Kahn et al. 2004	SC/SI/Miss	words	Re	SC > SI	none	b	none
Montaldi et al. 2006	1-4R	scenes	Re	R > all else	b	none	none
Sharot et al. 2004	RKN	scenes	Re	R > K	none	r	none
Weis et al. 2004b	SC/SI/Miss	scenes	Re	SC > SI	b	none	none
Wheeler & Buckner 2004	RKN	words	Re	R > K	b	none	none
Woodruff et al. 2005	RKN	words	Re	R > K	b	none	none
Yonelinas et al. 2005	1-4R	words	Re	R > 4	r	r	none
				Reported activations	16	11	2
				Total contrasts	19	19	19
				%	84%	58%	11%
B. Recollection of associations							
Jackson & Schacter 2004	Assoc. rec.	word pairs	En	Intact hit > intact called recombined	1	none	1
Kirwan & Stark 2004	Assoc. rec.	face-name	En	Intact hit > intact called recombined	r	r	none
Eldridge et al. 2005 ²	RKN	picture-word	Re	R > K	1*	none	b
Fenker et al. 2005	RKN	word-fearful face	Re	R > K	r	none	r
Fenker et al. 2005	RKN	word-neutral face	Re	R > K	b	1	none
Kirwan & Stark 2004	Assoc. rec.	face-name	Re	Intact hit > intact called recombined	r	r	b
				Reported activations	6	3	4
				Total contrasts	6	6	6
				%	100%	50%	67%
C. Familiarity							
Davachi et al. 2003	SC/SI/Miss	words	En	SC = SI > Miss	none	none	1
Gold et al. 2006	SC/SI/Miss	words	En	SC = SI > Miss	1	b	r
Henson et al. 1999	RKN	words	En	K > R	none	none	r
Kensinger & Schacter 2006	SC/SI/Miss	emotional pictures	En	SI > Miss	none	none	1
Kensinger & Schacter 2006	SC/SI/Miss	emotional words	En	SI > Miss	none	none	1
Kirwan & Stark 2004	Assoc. rec.	face-name	En	intact recognized > intact called new	none	r	r
Ranganath et al. 2003	SC/SI/1-6	words	En	1-4 linear increase	none	none	1
Uncapher & Rugg 2005	RKN	words	En	K > Miss	none	none	r
Uncapher et al. 2006	SC/SI/Miss	words+2 sources	En	All recognized > forgotten	none	none	1
Daselaar et al. 2006	1-6 conf	words	Re	1-6 linear decrease	1	none	1
Eldridge et al. 2005 ¹	RKN	picture-word	Re	RK < Miss = CR	r*	r	none
Gonsalves et al. 2005	RKN	faces	Re	R < K < Miss < CR	none	1	b
Montaldi et al. 2006	1-4R	scenes	Re	1-4 linear decrease	none	none	b
Weis et al. 2004b	SC/SI/Miss	scenes	Re	SI < Miss	none	none	r

Study	Method	Materials	Stage	Contrast	Hipp	PPHG	APHG
Yonelinas et al. 2005	1-4R	words	Re	1-4 linear decrease Reported activations Total contrasts %	b 4 15 27%	none 4 15 27%	none 13 15 87%

¹ Notes: Only experiments and contrasts that reported activation in at least one MTL subregion were included in the table. Also, contrasts not specific to familiarity or recollection (see text) were excluded. Numbers 1-6 refer to recognition confidence ratings, in which higher ratings indicate higher confidence that an item was studied. Abbreviations: SC, source (and item) correct; SI, source incorrect but item correct; Miss, old item judged new; Assoc. rec., associative recognition; R, remember; K, know; N, new; En, encoding; Re, retrieval; l, left; r, right; b, bilateral.

² This study used a flat-mapping procedure to differentiate activations in different hippocampal subregions. Although data were collected during encoding and retrieval, the encoding data were contaminated by an unexplained artifact that precludes a clear interpretation of the data. Accordingly, only the retrieval data are summarized here. Within the hippocampus, recollection-related activation was reported for the left subiculum, and familiarity-related activation was reported for the CA2/CA3/dentate gyrus region.