Commentary

Different Functions for Different Medial Temporal Lobe Structures?

Alison R. Preston and John D.E. Gabrieli[1]

Department of Psychology, Stanford University, Stanford, California 94305, USA

Since the landmark study of the globally amnesic patient H.M. by Scoville and Milner (1957), the essential role of the medial temporal lobes (MTL) in long-term memory has been well established. Considerable success has been made dissociating declarative memory processes (explicit memory for events and facts), which rely on the integrity of the MTL, from nondeclarative memory processes, which rely on other cortical, subcortical, and cerebellar structures (Gabrieli 1998). There has also been progress in distinguishing frontal-lobe and MTL contributions to declarative memory. Determining the precise contributions of the structures within the MTL to declarative memory, however, has proved challenging. The MTL is comprised of multiple structures including the hippocampal formation (the dentate gyrus, CA fields, and the subiculum), the amygdala, entorhinal cortex, and surrounding perirhinal and parahippocampal cortices. The focal role of the amygdala in the emotional modulation of memory appears clear (Phelps and Anderson 1997), but there is little consensus about how to characterize the differential contributions of specific MTL structures to declarative memory. Isolating the function of each of these structures, however, is central to understanding declarative memory processing and how damage or disease disrupts such processing.

Different MTL structures must be mediating different component processes underlying declarative memory, but the unanswered question is what are those different processes? One emerging idea about differential functions within the MTL is that the hippocampal formation is necessary for declarative memory tasks that require the processing of relations between multiple stimuli, whereas surrounding cortices mediate performance on tasks that rely on stimulus familiarity (or the converse, novelty). This hypothesis is consistent with the hierarchical connectivity of this region (Fig. 1A). Information from unimodal and polymodal association cortices enters the MTL through the perirhinal and parahippocampal cortices, which project to the entorhinal cortex, which in turn provides the major input to the hippocampal formation. This connectional anatomy suggests that the representational capacity of the perirhinal and parahippocampal cortices may be highly related to the incoming sensory information. These cortices may mediate familiarity-based memory processes linked to sensory aspects of items. In contrast, the hippocampus may generate a more abstract representation that integrates or binds multiple cortical sources of information, which is an important aspect of relational memory processes.

According to this view, the degree to which a memory task recruits relational versus familiarity processes would determine its relative reliance on hippocampal versus nonhippocampal MTL structures. Tasks that rely greatly on relational processing, such as paired-associate learning, would be greatly impaired by damage to the hippocampal formation. In contrast, tasks that can be performed on the basis of stimulus familiarity, such as tests of item recognition, could be supported by the function of the surrounding MTL cortices in the absence of hippocampal function. Several convergent findings have supported this hypothesis, including evidence from lesion and electrophysiological studies in animals (for review, see Brown and Aggleton 2001; Eichenbaum 2001), and from neuropsychological (Vargha-Khadem et al. 1997), and neuroimaging (Eldridge et al. 2000; Yonelinas et al. 2001) studies in humans.

A provocative challenge to this idea is set forth in a study by Stark et al. (2002) examining amnesic patients with bilateral MTL lesions thought to be limited to the hippocampal formation. By using patients with well-characterized lesions, the authors add an important contribution to the ongoing efforts to characterize MTL function in declarative memory. Examining patients with focal hippocampal damage allows the authors to test how damage to this structure affects memory tasks that differentially require relational and familiarity processing. In this study, hippocampal patients performed both single-item and associative recognition tasks. For single-item recognition, patients studied pictures of single faces or houses and after a delay, performed a yes/no recognition memory judgment. For associative recognition, patients studied face-house paired associates and after a delay, were presented with pairs of items. In this associative task, patients had to discriminate items that had been studied together (intact pairs) from items that had not been studied together (recombined pairs).

These tasks differentially focus on the processing of relations between test items compared with the processing

[1]**Corresponding author.**
E-MAIL gabrieli@psych.stanford.edu; FAX (650) 725-5699.
Article and publication are at http://www.learnmem.org/cgi/doi/10.1101/lm.54702.

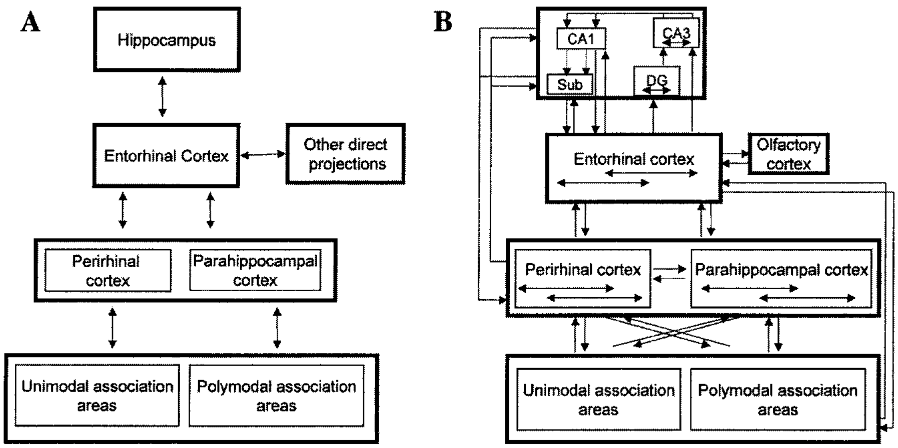

Figure 1 (*A*) Schematic diagram of the projections within the medial temporal lobe. (*B*) A more detailed diagram of medial temporal lobe connectivity including interconnections within and between structures. Adapted from Lavenex and Amaral (2000).

of the relative familiarity of test items. Single-item recognition can be performed on the basis of item familiarity because previously studied items are more familiar than new items, allowing subjects to endorse the more familiar items as having been studied (Yonelinas 2001). The use of novel faces and houses enhances the salience of familiarity, such that any sense of familiarity could only have been gained in the study phase and the foils are completely unfamiliar. In contrast, the associative memory test in this study attempts to eliminate the contribution of familiarity processes by presenting only previously studied items at test. The difference between intact and recombined pairs is then not likely to be due to the relative familiarity of the items, because all items have been studied, but rather to the arbitrary study-phase association between those items. Thus, these two recognition tests are meant to dissociate familiarity and relational processes posited to rely differentially on the contributions of the perirhinal cortex and hippocampal formation, respectively.

On the basis of this hypothesis, the relational/familiarity distinction predicts that patients with focal hippocampal damage would be selectively or disproportionately impaired on associative recognition, but exhibit intact or less-impaired performance on single-item recognition. However, patients with selective hippocampal damage were equally impaired on the single-item and associative recognition tasks. The impairments on the two tasks remained equal even when the overall performance of the patients was equated with healthy controls by increasing the patients' exposure to the study materials. The fact that the accuracy remained proportional at different levels of performance helps address the measurement problems inherent in comparing performances on two tasks that differ in difficulty (subjects performed more accurately on the single-item than the associative recognition test).

These results suggest that the hippocampal formation contributes similarly to declarative memory tasks that require relational or familiarity processing. These findings are supported by other electrophysiological, neuropsychological, and neuroimaging studies (Manns and Squire 1999; Wood et al. 1999; Stark and Squire 2000, 2001). Much conflicting evidence exists regarding the function of different MTL structures, and it is unclear whether such conflicts result from limits in the current experiments and methods used to answer such questions or whether they result from limits in current conceptions regarding what these structures contribute to declarative memory processing. Neuropsychological studies of patients with MTL lesions may be limited for a variety of reasons. In vivo structural imaging, even when carefully conducted, has limited resolution. Further, the patients in this study had hippocampal volume reductions ranging from 22% to 46%, raising the possibility that some memory processes mediated by the hippocampal formation were at least partially spared. In addition, double dissociations between the functions of different MTL structures have been impossible to examine because there are no reported patients who have intact hippocampal function in the presence of damage to the parahippocampal gyrus. Electrophysiological and lesion studies in animals also have methodological challenges, because it is unclear in most cases how the tasks used with animals to model declarative memory function are similar to those used to assess declarative memory in humans. Limits in the current spatial and temporal resolution of neuroimaging methods also prohibit a precise understanding of the function of the different MTL structures. Thus, it is likely that many convergent studies using a variety of methods will be necessary to gain clearer understanding of the different functions of multiple MTL substructures.

However, our understanding of the MTL may not only be limited by methodological challenges, but also by conceptual challenges. Stark, Bayley, and Squire (2002) suggest that simple dichotomies such as associative and nonassociative processes are unlikely to be successful at distinguishing the functional role of the hippocampal formation from the surrounding structures. Although assigning a specialized relational memory capacity to the hippocampal formation and a specialized familiarity or item-based memory capacity to the surrounding structures can account for many findings, it cannot explain others including the result published here by Stark, Bayley, and Squire (2002). Unlike the clear dissociations present between declarative and nondeclarative memory systems, there may not be simple or absolute dissociations between different MTL structures. The hierarchical and highly interconnected anatomy of MTL structures (Lavenex and Amaral 2000; Fig. 1B) may make it difficult to articulate simple distinctions in processing and necessitate more computational approaches for characterizing distinctions among MTL processes (O'Reilly and Rudy 2001).

Alternatively, this patient study may constrain a more precise definition of relational processing in the hippocampus. It has been suggested that the hippocampus is essential for encoding relations between experiences, rather than multiple elements of a single experience (Eichenbaum 2001). According to this view, the pairings between faces and houses are associations between elements of a single experience, and thus involve a different kind of binding than that which can occur between temporally distinct experiences. Some studies with rats support this interpretation of relational processing in the hippocampus (Bunsey and Eichenbaum 1996), but there is not yet compelling evidence on this point in humans.

Regardless of methodological and conceptual limitations, examining the function of the component structures of the MTL is an important question in memory research and critical to understanding how the brain mediates declarative memory processes.

ACKNOWLEDGMENTS

We thank Howard Eichenbaum and Andy Yonelinas for thoughtful comments. The authors are supported by National Institute of Health Grants MH59940, MH63576, and NS26985.

REFERENCES

Brown, M.W. and Aggleton, J.P. 2001. Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nat. Rev. Neurosci.* **2:** 51–61.

Bunsey, M. and Eichenbaum, H. 1996. Conservation of hippocampal memory function in rats and humans. *Nature* **379:** 255–257.

Eichenbaum, H. 2001. A cortical-hippocampal system for declarative memory. *Nat. Rev. Neurosci.* **1:** 41–50.

Eldridge, L.L., Knowlton, B.J., Furmanski, C.S., Bookheimer, S.Y., and Engel, S.A. 2000. Remembering episodes: A selective role for the hippocampus during retrieval. *Nat. Neurosci.* **3:** 1149–1152.

Gabrieli, J.D.E. 1998. Cognitive neuroscience of human memory. *Annu. Rev. Psychol.* **49:** 87–115.

Lavenex P. and Amaral, D.G. 2000. Hippocampal-neocortical interaction: A hierarchy of associativity. *Hippocampus* **10:** 420–430.

Manns, J.R. and Squire, L.R. 1999. Impaired recognition memory on the Doors and People Test after damage limited to the hippocampal region. *Hippocampus* **9:** 495–499.

O'Reilly, R.C. and Rudy, J.W. 2001. Conjunctive representations in learning and memory: Principles of cortical and hippocampal function. *Psychol. Rev.* **108:** 311–345.

Phelps, E.A. and Anderson, A.K. 1997. Emotional memory: What does the amygdala do? *Curr. Biol.* **7:** R-311–R-314.

Scoville, W.B. and Milner, B. 1957. Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosur. Psychia.* **20:** 11–21.

Stark, C.E. and Squire, L.R. 2000. Functional magnetic resonance imaging (fMRI) activity in the hippocampal region during recognition memory. *J. Neurosci.* **20:** 7776–7781.

———. 2001. Simple and associative recognition memory in the hippocampal region. *Learn. Mem.* **8:** 190–197.

Stark, C.E.L., Bayley, P.J., and Squire, L.R. 2002. Recognition memory for single items and for associations is similarly impaired following damage to the hippocampal region. *Learn. Mem.* **9:** 238–242.

Vargha-Khadem, F., Gadian, D.G., Watkins, K.E., Connelly, A., Van Paesschen, W., and Mishkin, M. 1997. Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* **277:** 376–380.

Wood, E., Dudchenko, P., and Eichenbaum, H. 1999. The global record of memory in hippocampal neural activity. *Nature* **397:** 613–616.

Yonelinas, A.P. 2001. Components of episodic memory: The contribution of recollection and familiarity. *Phil. Trans. R. Soc. Lond.* **356:** 1–12.

Yonelinas, A.P., Hopfinger, J.B., Buonocore, M.H., Kroll, N.E., and Baynes, K. 2001. Hippocampal, parahippocampal and occipital-temporal contributions to associative and item recognition memory: An fMRI study. *Neuroreport* **12:** 359–363.