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REVIEW

The Episodic Memory System: Neurocircuitry and Disorders

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The ability to encode and retrieve our daily personal experiences, called episodic memory, is supported by the circuitry of the medial temporal lobe (MTL), including the hippocampus, which interacts extensively with a number of specific distributed cortical and subcortical structures. In both animals and humans, evidence from anatomical, neuropsychological, and physiological studies indicates that cortical components of this system have key functions in several aspects of perception and cognition, whereas the MTL structures mediate the organization and persistence of the network of memories whose details are stored in those cortical areas. Structures within the MTL, and particularly the hippocampus, have distinct functions in combining information from multiple cortical streams, supporting our ability to encode and retrieve details of events that compose episodic memories. Conversely, selective damage in the hippocampus, MTL, and other structures of the large-scale memory system, or deterioration of these areas in several diseases and disorders, compromises episodic memory. A growing body of evidence is converging on a functional organization of the cortical, subcortical, and MTL structures that support the fundamental features of episodic memory in humans and animals.

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INTRODUCTION

Memory function is critical to daily life, and includes a variety of specific abilities that, at their core, enable information to be stored and retrieved over variable periods, ranging from seconds to days to years. Furthermore, it is now well recognized that there are multiple forms of memory; these are largely divided into kinds of memory that are typically expressed explicitly—that is, by direct conscious access to information (often called declarative memory)—and kinds of memory that are expressed implicitly through changes in behavioral or physiological responses in the absence of conscious access (nondeclarative memory). Nondeclarative memory and some declarative memory abilities are evolutionarily primitive, albeit elaborated at least to some degree in humans. By contrast, one particular form of declarative memory, called episodic memory, may be evolutionarily recent and its existence in animals is debated (Clayton *et al*, 2003). Here, we will briefly review these different forms of memory, then focus on the cognitive and neurobiological basis of episodic memory and its disorders.

MULTIPLE FORMS OF MEMORY

The domain of implicit or nondeclarative memory includes several forms of learning that occur during the performance of various tasks, and are typically expressed in enhanced or speeded behavioral performance or a change in behavioral choices or values. For example, procedural memory involves learning a sequence of movements or actions, such as swinging a golf club, riding a bicycle, or driving a car. Procedural learning depends on cortico-striatal systems and is compromised in disorders such as Parkinson's disease and Huntington's disease. Emotional memory involves a change in the approach to or avoidance of earlier neutral stimuli as a result of experience, such as in the acquisition of preference for a particular kind of food or aversion to objects with which one had an unpleasant experience. Emotional memory depends on subcortical and cortical

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interactions with the amygdala and is altered in panic disorders, phobias, and other neuropsychiatric disorders.

Declarative memory is also subdivided into multiple forms. Working memory involves the short-term maintenance of information in mind, and often the manipulation of that information for the purpose of achieving an immediate goal. The classic example is remembering a phone number while picking up and dialing a phone. However, working memory is also important for comprehending long written or spoken sentences, performing calculations, and holding in mind a string of new information or a series of movements. Performing multiple simultaneous tasks also requires working memory.

There are two forms of long-term declarative memory that both involve retrieving earlier stored information: semantic memory and episodic memory. Semantic memory involves memory for factual knowledge that has been learned, but for which specific 'time and place' information about the source of the original experience is typically not known. Encyclopedic knowledge of information such as the features of objects (eg, apples are usually red), categories (eg, oranges and bananas are both types of fruit), historical events, mathematical tables, cognitive maps, and similar types of information are considered to be stored in semantic memory systems of the brain.

Episodic memory involves the ability to learn, store, and retrieve information about unique personal experiences that occur in daily life. These memories typically include information about the time and place of an event, as well as detailed information about the event itself. The ability to describe the details of a recent holiday gathering or office meeting that took place in the previous weeks or months, for example, depends heavily on intact episodic memory function.

Studies of patients and then animals with focal brain lesions first illuminated distinctions between these multiple forms of memory and the different systems in the brain that subserve them. A brief historical survey will outline several of the early observations regarding amnesic syndromes and their localization.

THE NEUROLOGY AND NEUROPSYCHOLOGY OF EPISODIC MEMORY CIRCUITS

Traditional views of episodic memory circuits emerged largely from human case studies in neurology, neuropsychiatry, and neuropsychology. Animal research and recent human neuroimaging and memory disorders research have led to iterative revisions of these views, but many of these earlier patient-oriented studies provide an important foundation for understanding memory circuits in the brain.

EARLY CLINICAL CASES OF EPISODIC MEMORY LOSS

Although the experimental study of memory can be traced to Hermann Ebbinghaus, William James, and others in the last two decades of the 19th century, these approaches were neglected in patient studies until the famous studies of Brenda Milner and others starting in the 1950s. Before that, though, there were numerous case reports of memory disorders with enough clinical description and accompanying postmortem examination to illuminate some critical elements of the brain's memory networks.

Theodore Ribot, in *The Diseases of Memory* (1881), initially called attention to the nature and course of amnesia accompanying the dementias. He pointed out that the first characteristic of amnesia in patients with dementia is the loss of memory for recently experienced events with relative preservation of remote events, an observation later termed 'Ribot's law' in reference to the temporal gradient commonly observed in retrograde amnesias.

In the late 1880s and 1890s, Russian psychiatrist Sergei Korsakoff described a series of patients, mostly alcoholics, with a neuropsychiatric syndrome prominently involving memory loss. The characteristic amnesia, he observed, involved a disturbance of memory for recent events and new material, commonly with remarkably good memory for events occurring long before the illness, and often accompanied by a lack of insight into amnesia with confabulation. Patients often would repeat themselves in conversation, may not recognize the examiner from one encounter to the next, or might reconstruct an encounter with the examiner in a context that never took place.

Simultaneously with but separately from Korsakoff, German psychiatrist and pathologist Carl Wernicke described an acute clinical syndrome involving gait ataxia, opthalmoparesis, and confusion that sometimes evolved into chronic amnesia. Wernicke's encephalopathy and Korsakoff's amnesia eventually came to be recognized as different manifestations of a similar underlying condition. Wernicke's studies of the brains of his patients led to the observation that brainstem pathology was present in the vicinity of the third ventricle, and subsequent investigations by Gudden, Gamper, and others clarified the involvement of the mammillary bodies and dorsomedial nucleus of the thalamus. However, it was also clear from diminished brain weight that more than just those small regions were damaged, leading to hypotheses about cortical involvement.

Other brain regions now known to be importantly involved in episodic memory had roots in early neurologic literature, including Arnold Pick's (early 1900s) and Kahn and Thompson's observations in the 1930s that frontal lobe degeneration led to difficulties accessing 'memory material that may be there,' and Yakovlev and Locke's observations on the thalamus and cingulate cortex in the 1960s.

In 1907, German psychiatrist and neuropathologist Alois Alzheimer reported the case of a patient who died at age 51 after progressive memory loss and cognitive change, as well as personality and behavioral decline. Application of new histologic techniques identified plaques and tangles, the hallmark pathologic features of Alzheimer's disease (AD). As these pathological features became scrutinized in further studies, it became clear from Fuller's work in the early 1900s

and from Henderson and Machlachlan's work in the 1930s, as well as others, that the hippocampal formation was prominently affected.

Although Brown and Schafer had demonstrated experimentally in the 1880s that monkeys with temporal lobe lesions had impaired memory, it was Russian psychiatrist Vladimir Bekhterev who, in 1900, first reported medial temporal lobe (MTL) (uncinate gyrus and hippocampal) softening in a 40-year-old patient who died after exhibiting a profound amnesia. Fifty years later, a handful of other case reports of patients with amnesic syndromes and hippocampal pathology emerged (eg, Glees and Griffith, 1952).

In 1954, Connecticut neurosurgeon William Scoville reported the profound memory loss that occurred in two patients on whom he had performed the same surgical procedure, in one to treat psychosis and in the other to treat a refractory seizure disorder (Scoville, 1954). The surgical procedure involved the bilateral resection of the rostral MTLs, including the hippocampal formation, amygdala, and overlying cortex. Both patients developed profound amnesia, although because of emotional symptoms in the former patient the memory deficit was most obvious in the latter patient, HM.

Scoville and Brenda Milner—an English psychologist who had recently completed her training at McGill under Canadian psychologist Donald Hebb—reported in 1957 a series of 10 cases from Scoville's practice of temporal lobe resections (Scoville and Milner, 1957). Of these cases, three were described as having a severe memory deficit—all had undergone bilateral MTL resections including the hippocampal gyrus. They were described as forgetting 'the incidents of their daily life as fast as they occur.' The striking thing about Case 1, HM, was that his memory deficit was not only profound, including both anterograde and retrograde components with preservation of remote memory, but also isolated in the sense that other aspects of his intellect and personality were spared. Figure 1 shows HM's surgical lesion.

Besides calling prominent attention to the role of the MTL in memory function, it is important to recognize that many critical observations and hypotheses regarding episodic and other forms of memory were generated through studies of a man who became one of the world's most famous neurologic patients, HM, who died on December 4, 2008, at the age of 82 (Squire, 2009). Studies that were initiated in work with him by Brenda Milner, Suzanne Corkin, and many others led to the development of methods for measuring memory dysfunction and to seminal concepts regarding memory as a distinct, separable, localizable ability, and the brain's multiple memory systems, which are summarized extensively elsewhere (Eichenbaum and Cohen, 2001). HM and the other early case studies also provided the initial characterization between forms of declarative memory. Thus, HM, the patients of Bekhterev, those with Korsakoff's amnesia, and patients in the early stage of AD all exhibit severe deficits in episodic memory, that is, greatly diminished ability to remember daily personal events. These findings, and in particular the work with HM that highlighted a critical role for the medial temporal area in episodic memory, provided strong motivation to develop animal models of amnesia that could better identify the critical brain areas within the MTL and the functional circuitry within and outside that area. In the following sections we will review the results of these anatomical studies as well as behavioral and physiological findings from the animal literature, then return to modern studies of the cognitive neuroscience of episodic memory in humans.

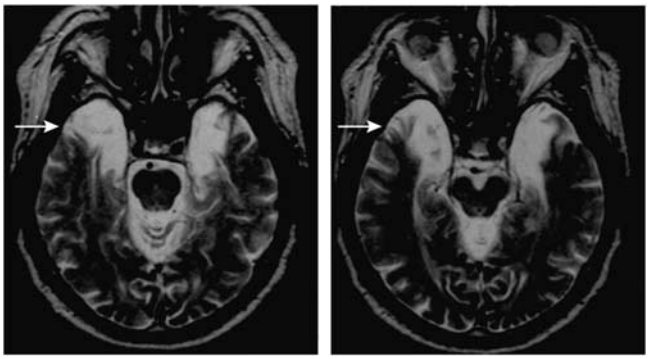

Figure 1. Two sections from a transverse MRI of HM's brain illustration location of surgical lesion, which involved the excision of the rostral portion of bilateral medial temporal lobes (arrows; areas of bright signal indicate cerebrospinal fluid). Figure courtesy of Professor Suzanne Corkin.

NEUROCIRCUITRY OF EPISODIC MEMORY: PERSPECTIVES FROM ANIMAL RESEARCH ANATOMY

Episodic memory is supported by a large network of brain areas, including widespread neocortical association areas and components of the MTL including both the parahippocampal cortical areas and the hippocampus. The anatomical organization of the major pathways of interaction between the neocortex and the medial temporal areas, as well as the organization of medial temporal areas themselves, is also largely conserved across mammalian species from rodents to primates (Amaral and Witter, 1995; Manns and Eichenbaum, 2006; Witter *et al*, 2000).

The general organization of this system is that virtually all neocortical association areas send projections that converge onto the parahippocampal cortical areas surrounding the hippocampus, which in turn, projects onto each subdivision of the hippocampus. The hippocampal subdivisions are internally connected by a serial, unidirectional path, starting with the dentate gyrus, and continuing through CA3, then CA1, and then the subiculum. The cortical outputs of hippocampal processing, arising in CA1 and subiculum, involve feedback connections back to the parahippocampal region, which projects back to the neocortical association areas from which the inputs to the medial temporal area originated. This organization

suggests a central role in organizing or extending the persistence of cortical representations (Eichenbaum, 2000). Neocortical areas contribute to declarative memory through various aspects of cognitive and perceptual processing and memory-associated plasticity in these areas likely constitute the permanent storehouse of declarative memories. The MTL, unlike neocortical areas, has a fully selective function in memory and not other cognitive or perceptual functions. Therefore, we will briefly identify the cortical components of this system across mammalian species then focus on the anatomy and functional organization of the MTL, with particular emphasis on the role of the hippocampus. Figure 2 provides a schematic of the major brain regions described.

Neocortical Areas

The neocortical areas involved in episodic memory include the prefrontal cortex and other areas that mediate working memory, effortful retrieval, source monitoring, and other cognitive processing functions that are essential to conscious recollection (Buckner and Wheeler, 2001; Dobbins *et al*, 2002; Farovik *et al*, 2008). In addition, areas of the parietal and temporal cortex are involved in complex perceptual processing essential to contents of information that is the subject of recollection (Uncapher *et al*, 2006). The architecture and functional organization of neocortical regions involved in episodic memory differ substantially among mammalian species. For example, there are numerous dissimilarities in the neocortex that reflect general differences between small-brained and big-brained mammals, such as cortical size, laminar stratification, and number of polymodal association areas (Krubitzer and Kaas, 2005; Manns and Eichenbaum, 2006). Further, the extent of cortical areas devoted each sensory modality also varies substantially between species. However, despite these substantial distinctions among species, there is remarkable similarity in the pathways and interactions between neocortical association areas and the MTL. Thus, in all mammalian species, projections from all neocortical association areas strongly converge onto the MTL, which also sends strong projections back to the same cortical association areas.

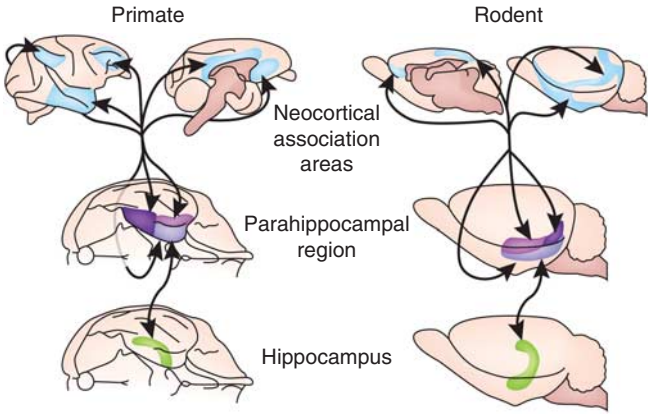

Figure 2. The anatomy of the medial temporal lobe memory system (Eichenbaum, 2000). In both monkeys and rats the origins of specific information to the hippocampus include virtually every neocortical association area. Each of these neocortical areas (blue) projects to one or more subdivisions of the parahippocampal region, which includes the perirhinal cortex (purple), the parahippocampal (or postrhinal) cortex (dark purple), and the entorhinal cortex (light purple; Burwell *et al*, 1995; Suzuki, 1996). The subdivisions of the parahippocampal region are interconnected and send major efferents to multiple subdivisions of the hippocampus itself (green), the dentate gyrus, the CA3 and CA1 areas, and the subiculum. Thus, the parahippocampal region serves as a convergence site for cortical input and mediates the distribution of cortical afferents to the hippocampus. Within the hippocampus, there are broadly divergent and convergent connections that could mediate a large network of associations (Amaral and Witter, 1989). The outcomes of hippocampal processing are directed back to the parahippocampal region, and the outputs of that region are directed in turn back to the same areas of the cerebral cortex that were the source of inputs to this region (Burwell *et al*, 1995; Suzuki, 1996). There are additional structures that have been included as components of this system, including medial diencephalic structures that connect with the hippocampus along with other subcortical areas, through a major fiber bundle called the fornix (Aggleton and Brown, 1999).

Parahippocampal Region

Outputs of neocortical association areas are funneled into the hippocampus through the parahippocampal region, an interconnected set of medial temporal cortical areas surrounding the hippocampus. These areas include the perirhinal cortex, the parahippocampal cortex (called postrhinal cortex in rodents), and the entorhinal cortex, and the cytoarchitecture and the interconnectivity among these areas is also remarkably similar across mammalian species (Burwell *et al*, 1995). In addition, parallel pathways arise in the perirhinal and parahippocampal cortices and terminate in the hippocampus similarly through two partially distinct channels (Burwell and Amaral, 1998a; Suzuki and Amaral, 1994). The perirhinal cortex receives inputs from areas concerned with identifying the nonspatial identity of stimuli, whereas the parahippocampal cortex receives inputs from many areas involved in processing the spatial content of sensory information. For example, the monkey perirhinal cortex receives more inputs from areas along the ventral visual pathway thought to be important for object recognition, the parahippocampal cortex receives more inputs from areas along the dorsal visual stream thought to be important for visually guided actions (Suzuki and Amaral, 1994). In rodents, the visual system is not clearly segregated into ventral and dorsal visual streams, yet the perirhinal and postrhinal cortices receive disproportionate nonspatial and spatial information, respectively (Burwell and Amaral, 1998b). For example, the rodent perirhinal cortex receives prominent inputs from the polymodal ventral temporal association area (TEv). In contrast, the postrhinal cortex instead receives prominent spatial inputs from areas such as posterior parietal cortex. The separation of spatial and nonspatial information is partially maintained within the parahippocampal region until it is combined in the hippocampus. In both the rat and

the monkey, the perirhinal cortex tends to project more to the lateral entorhinal area (LEA) of the entorhinal cortex, and the parahippocampal cortex tends to project more to the medial entorhinal area (MEA, Witter *et al*, 2000).

Hippocampus

LEA and MEA send separate projections to the hippocampus. Both pathways project to each of the four hippocampal subregions, but the pattern in which the fibers from both pathways terminate in hippocampal targets differs between those arriving in CA3 and dentate gyrus and those in CA1 and subiculum, such that information passing through LEA and MEA is combined on the same neurons in the dentate gyrus and CA3 but arrives in separate neuronal populations in the subiculum and CA1, an pattern of organization that may support the ability of the hippocampus to both associate and distinguish events and the context in which they appear (Witter *et al*, 2000).

This anatomical data provide potentially important insights into basic mechanisms that underlie the capacity for episodic memory. Thus, across species, most of the neocortical input to the perirhinal cortex comes from association areas that process unimodal sensory information about qualities of objects (ie, 'what' information), whereas most of the neocortical input to the parahippocampal cortex comes from areas that process polymodal spatial ('where') information (Burwell *et al*, 1995; Suzuki and Amaral, 1994). There are connections between the perirhinal cortex and parahippocampal cortex, but the 'what' and 'where' streams of processing remain largely segregated as the perirhinal cortex projects primarily to the LEA whereas the parahippocampal cortex projects mainly to the MEA. Similarly, there are some connections between the entorhinal areas, but the 'what' and 'where' information streams mainly converge within the hippocampus. These anatomical considerations suggest a functional organization of the flow of information into and out of the hippocampus, which we will outline next.

EXPERIMENTAL MODELS OF THE FUNCTIONAL ORGANIZATION OF THE EPISODIC MEMORY SYSTEM

The anatomical evidence just described suggests functional distinctions between medial temporal regions that are confirmed by substantial evidence from studies on the effects of selective damage to these areas and by characterizations of the firing properties of neurons in these areas.

Perirhinal and Lateral Entorhinal Cortex

Substantial evidence from studies on animals indicates that neurons in the perirhinal cortex and lateral entorhinal cortex are involved in the representation of and memory for individual perceptual stimuli. Electrophysiological studies on monkeys and rats performing simple recognition tasks have shown that many cells in the perirhinal cortex exhibit enhanced or suppressed responses to stimuli when they re-appear in a recognition test (Suzuki and Eichenbaum, 2000). Complementary studies in animals with damage to the perirhinal cortex indicate that this area may be critical to memory for individual stimuli in the delayed nonmatching to sample task in rats (Otto and Eichenbaum, 1992) and monkeys (Suzuki *et al*, 1993). These and other data have led several investigators to the view that the perirhinal cortex is specialized for identifying the strength of memories for individual stimuli (Brown and Aggleton, 2001).

Parahippocampal and Medial Entorhinal Cortex

The parahippocampal cortex and MEA may be specialized for processing spatial context. Although perirhinal and lateral entorhinal neurons have poor spatial coding properties, parahippocampal and medial entorhinal neurons show strong spatial coding (Hargreaves *et al*, 2005). Correspondingly, though object recognition is impaired after perirhinal damage, object-location recognition is deficient after parahippocampal cortex damage in rats (Gaffan *et al*, 2004) and monkeys (Alvarado and Bachevalier, 2005). Similarly, perirhinal cortex damage results in greater impairment in memory for object pairings whereas parahippocampal cortex lesions result in greater impairment in memory for the context in which an object was presented (Alvarado and Bachevalier, 2005).

Hippocampus

Recent studies using sophisticated signal detection analysis have shown that, as in humans, in rodents recognition memory is supported by a combination of familiarity for previously experienced stimuli and recollection of specific episodes involving those stimuli, and the recollective component of recognition memory depends on the hippocampus (Fortin *et al*, 2004; Sauvage *et al*, 2008). In addition, corresponding to the commonly held view that episodic recollection involves memory for the spatial and temporal context of specific experiences, several investigators have argued that animals are indeed capable of remembering the context in which they experienced specific stimuli, and that this capacity also depends on the hippocampus (Clayton and Dickinson, 1998; Day *et al*, 2003). For example, Ergorul and Eichenbaum (2004) developed a task that assesses memory for events that involve the combination of an odor ('what'), the place in which it was experienced ('where'), and the order in which the presentations occurred ('when'). On each of a series of events, rats sampled an odor in a unique place along the periphery of a large open field. Then, memory for when those events occurred was tested by presenting a choice between an arbitrarily selected pair of the odor cups in their original locations. Analyses of the data on these choices plus other probe tests showed that rats normally use a combination of 'where' and 'what' information to judge 'when' the events

occurred whereas rats with hippocampal damage cannot effectively combine 'what', 'when', and 'where' qualities of each experience to compose the retrieved memory. Figure 3 provides an illustration of this model.

Consistent with these findings, many studies have shown that hippocampal neurons encode many features of events and the places where they occur (Eichenbaum, 2004). For example, in one study, rats performed a task in which they had to recognize any of nine olfactory cues placed in any of nine locations (Wood *et al*, 1999). As the location of the discriminative stimuli was varied systematically, cellular activity related to the stimuli and behavior could be dissociated from that related to the animal's location. Some hippocampal cells encoded particular odor stimuli, others were activated when the rat sampled any odor at a particular place, and yet others fired associated with whether the odor matched or differed from the earlier cue. However, the largest subset of hippocampal neurons fired only associated with a particular combination of the odor, the place where it was sampled, and the match–nonmatch status of the odor. Another study examined the firing properties of hippocampal neurons in monkeys performing a task in which they rapidly learned new scene–location associations (Wirth *et al*, 2003). Just as the monkeys acquired a new response to a location in the scene, neurons in the hippocampus changed their firing patterns to become selective to particular scenes.

The combination of findings from the anatomy and functional characterizations in animal models are consistent with the anatomically guided hypothesis about the functional organization of the hippocampal system and suggest mechanisms by which the anatomical components of this system interact in support of the phenomenology of episodic recollection. After experience with a stimulus, the perirhinal and LEAs may match a memory cue to a stored template of the stimulus, reflected in suppressed activation that may signal the familiarity of previously experienced stimuli but does not provide information about where or when it was experienced. Outputs from perirhinal and LEAs back to neocortical areas may be sufficient to generate the sense of familiarity without participation of the hippocampus. In addition, during the initial experience, information about the to-be-remembered stimulus, processed by the perirhinal and LEAs, and about the spatial and possibly nonspatial context of the stimulus, is processed by the parahippocampal and MEAs, converge in the hippocampus. During subsequent retrieval, presentation of the cue may drive the recovery of object-context representations in the hippocampus that, through back projections, regenerates a representation of the contextual associations in parahippocampal and MEAs, which cascades that information back to neocortical areas that originally processed the item and contextual information. This processing pathway may constitute a principal mechanism for episodic recollection of unique events across species (Eichenbaum *et al*, 2007). Notably, there are also direct connections between perirhinal and parahippocampal cortex and between zones of the entorhinal cortex (Burwell *et al*, 1995; Suzuki and Amaral, 1994). One possibility is that these connections are strengthened over time after learning through reactivations that involve loops through the hippocampus, and these connections within cortical areas might support a gradual consolidation of memories in those cortical areas (Eichenbaum *et al*, 1999); this mechanism could explain why retrograde amnesia reaches farther back in time when damage to the MTL includes cortical areas in addition to the hippocampus (Rempel-Clower *et al*, 1996).

As described below, studies on humans have shown that a specific set of neocortical areas beyond the MTL also has important functions in episodic memory. Studies of the role in episodic memory of neocortical areas are far less developed in animals. However, recent evidence suggests that at least some cortical areas may also have a critical function in episodic memory in animals. In one such study, rats with damage to the prefrontal cortex were tested on recognition memory using signal detection analysis

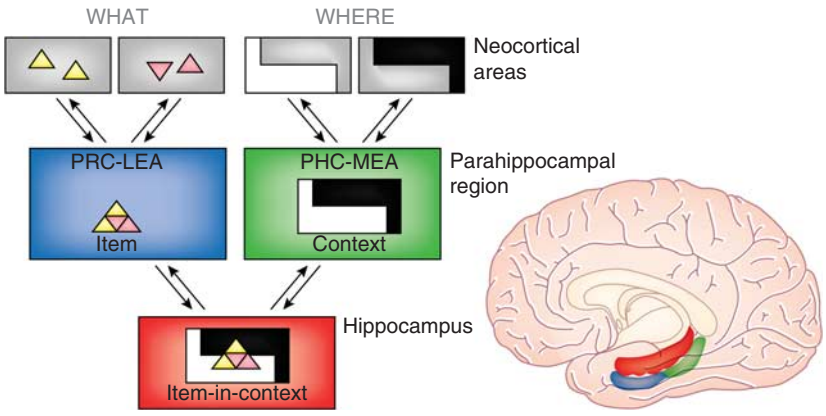

Figure 3. A proposed functional organization of the medial temporal lobe memory system (Eichenbaum *et al*, 2007). Neocortical input regarding the object features ('what') converges in the perirhinal cortex (PRC) and lateral entorhinal area (LEA), whereas details about the location ('where') of objects 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.

methods (Farovik *et al*, 2008). The results showed that damage to the prefrontal cortex results in a selective deficit in recollection with spared familiarity, similar to the effects of damage to the hippocampus. However, the detailed pattern of performance characterized in the signal detection analyses showed that the nature of the recollection impairment after prefrontal damage was different from that after hippocampal damage. Specifically, damage to the hippocampus resulted in forgetting of items previously seen in the study phase, whereas damage to the prefrontal cortex resulted in false-positive responses to items that were not seen in the study phase but were experienced in prior study lists. Thus, as in humans, the prefrontal cortex may have a selective function in episodic memory by monitoring and selecting retrieved memories.

AGING

Cognitive aging involves the deterioration of higher order intellectual capacities associated with deterioration of brain function. In humans, cognitive aging most prominently involves a decline in episodic memory, similar to what one might expect of a mild form of damage to the MTL area. The development of animal models of cognitive aging are based on studies of functions of the MTL structures and, in particular, the hippocampus. These studies have indeed shown that aged rats are impaired on tests of hippocampal spatial memory function, and that this cognitive impairment can be related to deterioration of neurobiologial markers of function within the hippocampus (Gallagher and Rapp, 1997; Wilson *et al*, 2006).

In addition, a recent study has have offered an approach to specifically assess episodic recollection in aging animals, using a signal detection analysis of recognition memory that has distinguished age-associated deficits in episodic recollection *vs* relatively intact familiarity in humans (Robitsek *et al*, 2008). This study used a combination of behavioral assessments in the Morris water maze task and signal detection analyses of recognition memory to show several parallels between cognitive aging in rodents and humans that strengthen the animal model. First, aged rats showed a considerable variability in the severity of their spatial and recognition memory impairments. Second, the age-associated deficit in recognition memory was isolated to impairment in episodic recollection and not familiarity. Third, some aged rats compensated for the deficit in episodic recollection by using a compensatory strategy of using intact familiarity as a basis for recognition. All of these findings support the hypothesis that cognitive aging has a common basis across species, providing a valid platform for exploring interventions that might alleviate age-associated memory disorder.

Additional neurophysiological studies on the firing patterns of hippocampal neurons suggest a network information processing failure that may underlie the deficit in recollection. These studies focus on hippocampal 'place cells', principal neurons in the hippocampus, which fire reliably when a rat is in a particular location in a familiar environment. When young rats subsequently explore a novel environment, the patterns of spatial firing of individual hippocampal neurons typically change, consistent with a distinct representation for the novel experience. However, place cells in aged rats often fail to change when the animal is exposed to a novel environment and instead often show the same spatial firing pattern as they did in the familiar environment, and this rigidity of spatial representation predicts the spatial memory impairment in the water maze (Wilson *et al*, 2006). This abnormality has been characterized as a failure in *pattern separation* of the contextual stimuli from the familiar and novel environments and a consequent tendency toward *pattern completion* of the representation of the familiar spatial context. Notably, this abnormality was selective to area CA3, the subfield of the hippocampus, which normally is inclined to strong pattern completion or separation (known as attractor dynamics) (Guzowski *et al*, 2004). One interpretation of these findings is that such a failure in pattern separation could also underlie the deficit in the episodic recollection component of recognition memory. Thus, failure to pattern separate distinct experiences would be expected to compromise the animal's ability to distinguish specific experiences with stimuli in the current list from that of prior appearances of the same stimuli in earlier lists. The result would be a catastrophic pattern of interference for the hippocampus and a consequent inability to recollect the experience of being presented with a specific item in this study list. This argument is speculative, but is consistent with the common observation of inappropriate intrusions of old memories associated with cognitive aging (Kahana *et al*, 2005). The extension of the rodent model into aspects of odor recognition memory allows for further examination of this and other hypotheses about the neurobiological bases of cognitive aging.

NEUROCIRCUITRY OF EPISODIC MEMORY: PERSPECTIVES FROM HUMAN NEUROIMAGING

The rapid development of neuroimaging techniques over the past couple decades has led to an explosion of research on episodic memory in humans. As many of these techniques are relatively noninvasive and widely available, investigators have been able to combine advanced anatomic and functional neuroimaging and other brain mapping methods with sophisticated experimental cognitive paradigms. Some of this work has confirmed and extended knowledge derived from animal research of the organization and roles of nodes of episodic memory neurocircuitry, whereas other work has probed memory-related abilities that are difficult to study in animals or thought to be uniquely human. In this section, human functional neuroimaging will be reviewed with a focus on the MTL memory

system, the isocortical memory system, and recent work attempting to explicitly investigate large-scale episodic memory networks. Relatively little functional neuroimaging work (with important exceptions, Shohamy and Wagner, 2008) has been performed on the contributions of thalamic, basal forebrain, and other subcortical regions to human episodic memory.

The Human Medial Temporal Lobe Episodic Memory System

Since the 1990s, positron emission tomography and functional magnetic resonance imaging (fMRI) experiments have demonstrated the 'activation' of the hippocampal formation and other MTL regions during the performance of episodic memory tasks. It is important to point out that the activation of a brain region as detected with functional neuroimaging methods is relative, as functional neuroimaging measures obtained during task performance are typically compared with measures obtained during a control condition, thus identifying relatively greater activity in one condition than another. Furthermore, co-registration techniques that are usually required to align data from multiple subjects to each other are imperfect but continue to be improved (Miller *et al*, 2005). From a conceptual standpoint, given the variability of MTL subregion size and shape between subjects, some investigators prefer to localize fMRI data at the individual subject level first and then perform statistical analyses, rather than trying to localize activity at the group level after aligning subjects to a template.

An important technical and experimental design development in the late 1990s, 'event-related' fMRI (drawn from event-related potential electroencephalographic methodology), enabled the detection of relatively greater hippocampal and other MTL activation during the encoding of stimuli that were subsequently remembered as compared with those that were not remembered (Burock *et al*, 1998). In the decade since the first papers showing relatively greater MTL activity during subsequently remembered items (Brewer *et al*, 1998; Wagner *et al*, 1998b), many clever experiments have built on this approach to elucidate specific functional neuroanatomic properties of MTL and other brain regions. Figure 4 highlights the data supporting these observations.

One issue that has been investigated since the early days of functional neuroimaging is the differential activation of the MTL during encoding as opposed to retrieval. Partly because of the large number of variables that often differ between experiments, there is still not consensus regarding whether there is a specific topographic organization in the MTL that differentiates the functional neuroanatomy of encoding or retrieval. Some investigators find that the rostral hippocampal formation is relatively more active during encoding whereas the caudal hippocampus is relatively more active during retrieval (Zeineh *et al*, 2003), but the opposite findings have also been observed (Gabrieli *et al*, 1997). Within the canonical MTL subregions, some investigators have found encoding-related activity in hippocampus-proper CA fields with retrieval-related activity in subiculum (Zeineh *et al*, 2003), whereas others have found a pattern that differs (Pihlajamaki *et al*, 2003).

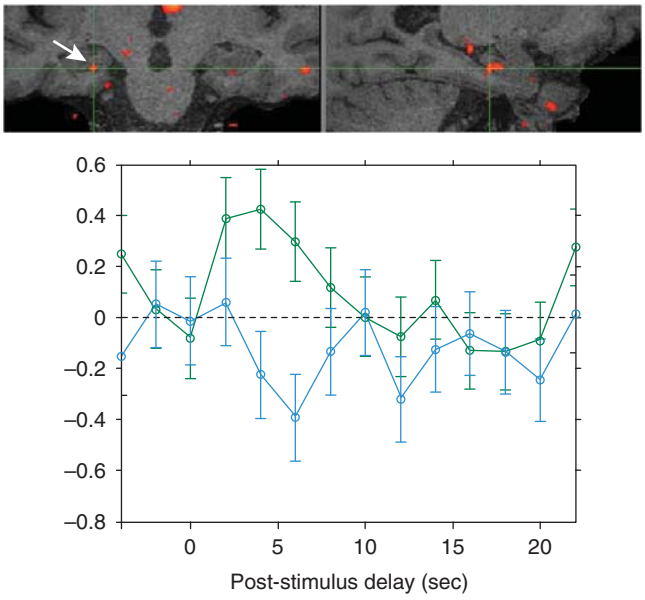

Figure 4. Functional MRI of 70-year-old individual during the encoding of new face-name pairs. Brain image shows localization of activation, which includes hippocampus (arrow and crosshair) and other medial temporal lobe regions. Crosshair shows localization of the area from which time course of blood-oxygen-level-dependent activity is derived, showing the signal for items that are subsequently correctly recognized (green, hits) *vs* items that are not correctly recognized (blue, misses).

A major challenge when trying to connect human with animal data regarding the MTL is the gap in resolution. The human functional neuroimaging technique with the highest spatial resolution, fMRI, is still striving to obtain resolution for differential effects on the order of 1 mm, with most studies at advanced centers still working in the 1.5–2 mm range. Furthermore, the signal-to-noise ratio of blood-oxygen-level-dependent (BOLD) fMRI in the MTL is notoriously poor. Technical advances being worked out at some centers are still badly needed for further advances that would bring human MTL imaging closer to animal data.

Questions related to the specificity of MTL regions for memory processes have been the subject of a number of studies, including associative *vs* item-based memory and the dual process model of episodic memory (recollection *vs* familiarity). Some evidence supports the concept that the hippocampal formation is selectively activated for recollection or for associative memories, and the perirhinal or entorhinal cortex is activated for familiarity or for item-based nonassociative memories (Davachi *et al*, 2003; Eichenbaum *et al*, 2007; Squire *et al*, 2004). However, other studies of these same topics have produced conflicting results (Squire *et al*, 2007).

The specificity of MTL regions for the particular content of episodic memory has received some attention. Successful memory for faces tends to be associated with activity in perirhinal and rostral hippocampal regions, whereas objects

tend to be associated with somewhat more caudal activity (Preston *et al*, 2009). Memory for indoor or outdoor scenes or other spatial context information is fairly reliably associated with posterior parahippocampal activity (Maguire, 1997; Stern *et al*, 1996). Surprisingly, little work has been performed on object-in-context associative memory performance, although one study distinguished activation of the hippocampus and posterior parahippocampal region associated with memory for objects in imagined contextual scenes from activation of the perirhinal cortex associated with memory for the objects alone (Davachi *et al*, 2003).

Neuroimaging investigations have recently turned to the remarkably fine-grained ability of components of the MTL memory system to form associations even in the absence of complete information, while at the same time distinguishing related but distinct objects or contexts from each other—pattern completion *vs* pattern separation, as described above. Similarly to rodent studies, initial experiments suggest that CA3 or dentate gyrus has an important function in pattern separation within the hippocampal formation (Bakker *et al*, 2008).

Recent neuroimaging research has begun to provide evidence convergent with animal data that the MTL may have specific functions in the flexible use of episodic memory trace information for processes that probably subserve inferential reasoning and generalization. Transitive inference, the ability to use previously learned associative relationships between items to draw inferences about probable associations that have never been specifically learned, seems to depend on the hippocampal formation (Dusek and Eichenbaum, 1997). Functional neuroimaging evidence also supports the specific role of the hippocampal formation in transitive inference in humans (Heckers *et al*, 2004).

The Human Isocortical Episodic Memory System

Although tremendous attention has been focused in human functional neuroimaging episodic memory experiments on the MTL memory system, the fundamental involvement of isocortical brain regions has been obvious since the first studies. It was initially not clear the extent to which ventrolateral temporal, medial and lateral parietal, and medial and lateral frontal regions supported activities necessary but not sufficient for the performance of encoding and retrieval tasks, including perceptual, lexical, semantic, attentional, control, or decision making activities. Many of these isocortical regions were commonly activated in memory imaging experiments. With the advent of subsequent memory paradigms, it became clear that a number of these areas seem to be active contributors to the process of learning and memory itself, as they are relatively more active during successful encoding and retrieval than during unsuccessful attempts. Human cortical regions engaged during memory encoding are shown in Figure 5.

Regions in the temporal lobe, which are outside the MTL, can be functionally engaged in subsequent memory paradigms. Although some of these activations may reflect material-specific or process-specific aspects of stimulus perception, reports of subsequent memory effects in some regions suggest that there may be specific roles in episodic memory. The ventral temporal cortex, including fusiform gyrus, is commonly engaged when pictures of visual objects are presented, and the lateral temporal cortex including superior temporal gyrus is typically engaged during the encoding of auditory information. Furthermore, consistent with hypotheses regarding re-activation of sensory cortex during memory retrieval, imaging experiments have demonstrated that subregions within sensory-specific temporal isocortical brain regions, which are engaged during encoding, are re-engaged during retrieval of sensory-specific information (Wheeler *et al*, 2000). In addition, the degree to which subjects report that they use strategies emphasizing visual features or visual relationships among items (as opposed to verbal strategies) to perform a memory task relates to the level of engagement of visual regions in the occipitotemporal cortex during encoding (Kirchhoff and Buckner, 2006).

Although early patient studies led some clinicians to posit that frontal lesions impair memory performance purely in a

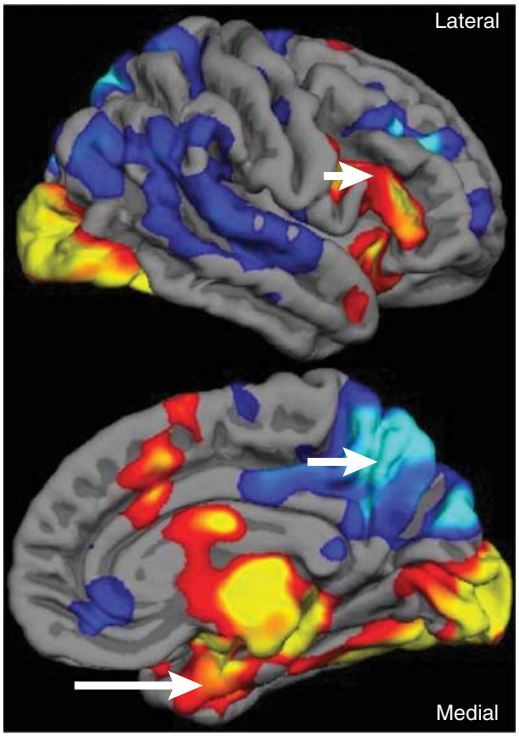

Figure 5. Functional MRI of a group of young human subjects during the encoding of novel pictures that are subsequently recalled, showing cortical regions involved in the large-scale episodic memory network and related areas. Red/yellow regions are activated (including ventrolateral prefrontal cortex (top image, arrow) and medial temporal cortex (bottom image, long arrow)) during the encoding of new pictures of objects, whereas blue regions are deactivated (including posterior cingulate/precuneus (bottom image, short arrow) below baseline.

secondary fashion through effects on attention, organization, and motivation (Hecaen and Albert, 1978; Luria, 1973), others have emphasized the primacy of the frontal lobes for memory, including delayed response, associative learning, and memory for temporal order (Milner, 1971; Milner *et al*, 1985; Petrides, 1985; Stuss *et al*, 1994). More recent clinical neuropsychological studies of memory function have shown multiple dissociations in memory impairment in patients with frontal lesions compared with MTL amnesics, including temporal order and source memory (Janowsky *et al*, 1989; Shimamura *et al*, 1990). Neuroimaging data have largely provided support for ideas initially developed in work with patients, indicating that frontal systems are important for the spontaneous use of strategies during encoding, the tagging of events with temporal and other contextual information, and search, monitoring, and other controlled processes during retrieval (Davidson *et al*, 2006).

The ventrolateral prefrontal cortex is uniformly involved in the encoding of information, with particular contribution of the left ventrolateral prefrontal cortex for semantic processing of information being encoded (Fletcher and Henson, 2001). The prominent leftward lateralization of encoding processes led to the generation of the 'HERA' model of memory, or 'hemispheric encoding/retrieval asymmetry' (Habib *et al*, 2003; Tulving *et al*, 1994a), which puts forth a process-specific outline accounting for the common findings of leftward activation during encoding and rightward activation during retrieval. Other accounts emphasize content-specific aspects of prefrontal function and memory, with left-lateralized ventrolateral activity for verbal material and right-lateralized activity for visual material (Wagner *et al*, 1998a).

Several prefrontal regions in both hemispheres have been shown in neuroimaging experiments to make distinct contributions to episodic memory retrieval. It is important to consider the variety of cognitive processes that have been proposed as relevant for retrieval (Rugg *et al*, 2002; Rugg and Wilding, 2000). First, preretrieval processing is thought to support the attempt to retrieve information in response to a cue, and theoretically including retrieval mode (the cognitive state or set subserving attempted retrieval), retrieval effort (level of difficulty involved in the task), and retrieval orientation (qualitatively different forms of processing of retrieval cues, such as recognition *vs* source judgements). Neuroimaging studies manipulating retrieval effort and orientation generally show modulation of anterior and ventrolateral regions of the left prefrontal cortex, whereas studies of retrieval mode have suggested the involvement of frontopolar cortex, possibly in a right-lateralized manner.

Postretrieval processing operates on the product of the retrieval attempt, and involves the monitoring and evaluation of retrieved information, ultimately resulting in a retrieval decision (Stevens and Grady, 2007). Right dorsolateral prefrontal cortex seems to be consistently involved in postretrieval processing. Finally, recently developed event-related fMRI experimental designs have begun to illuminate differential transient *vs* sustained contributions to memory retrieval, with evidence supporting the involvement of the right frontopolar cortex in retrieval mode and left dorsolateral prefrontal cortex in individual retrieval attempts (Velanova *et al*, 2003).

The roles of the posterior lateral and medial parietal cortices in episodic memory have received greater attention partly as a result of functional neuroimaging studies, which have consistently shown a variety of memory-related effects in these regions (Wagner *et al*, 2005). In the medial parietal regions, including posterior cingulate, precuneus, and retrosplenial cortex, and in the left lateral posterior parietal cortex, including inferior parietal lobule and to a lesser extent superior parietal lobule, there is a consistent increase in activity during the recognition of old, previously encountered items as compared with new items (Tulving *et al*, 1994b). This 'old–new' effect is also present for items falsely thought to be old (Kahn *et al*, 2004; Wheeler and Buckner, 2003), presumably reflecting the subjective experience of having previously encountered an object. Recent functional neuroimaging data are beginning to indicate that there may be functionally distinct subregions within the lateral parietal cortex, including possibly a region within the intraparietal sulcus that may reflect familiarity effects and an inferior parietal lobule region that may reflect detailed recollection (Wagner *et al*, 2005). Although it is clear that there are important primary and secondary afferent and efferent connections between parietal cortical regions and the MTL (Kobayashi and Amaral, 2003, 2007; Mesulam *et al*, 1977; Van Hoesen *et al*, 1972), increasing experimental attention is being devoted to the specific functional roles of parietal cortices in episodic memory and frontoparietal and parietotemporal interactions.

The Large-Scale Distributed Episodic Memory Network

Lesion and neuroimaging data are often focused on the contributions of one or more specific regions to task performance, although it is widely acknowledged that most abilities depend on large-scaled distributed brain networks (Mesulam, 1998). Prefrontal–temporal interactions have been a particularly attractive starting point for theoretical work in this area on episodic memory (Simons and Spiers, 2003). Although lesion analysis studies in monkeys and humans and other data have been used to develop hypotheses about large-scale distributed episodic memory networks, human neuroimaging data inherently provide fruitful data for analysis at the systems level. Besides the co-activation of brain regions during the performance of episodic encoding and retrieval tasks, as described above, new systems-level analytic approaches to functional neuroimaging data have begun to show the interactions between brain regions that make up the large-scale episodic memory network.

So-called functional connectivity neuroimaging data analytic approaches have existed for nearly a decade,

and have been applied in a few studies to questions related to the interaction between brain regions engaged in memory tasks. These approaches enable the detection of correlated activity increases between spatially distributed brain regions, and causal modeling using activity increases in one region to predict activity increases in another. These types of analyses have provided evidence for prefrontal–medial temporal–ventrolateral temporal interactions in episodic encoding that leads to successful subsequent free recall, for example (Dickerson *et al*, 2007).

A prominent line of functional neuroimaging research has identified a set of brain regions that are relatively more active during undirected epochs of time during experiments than during epochs involving the directed performance of a variety of tasks, including sensorimotor, attentional, language, and other types of tasks. These brain regions include posterior cingulate/precuneus, lateral inferior parietal lobule, lateral and medial temporal, and medial prefrontal cortices, and have been called the 'default mode' network (Buckner *et al*, 2008; Raichle *et al*, 2001). Many of these brain regions are activated during various processes involved in specific memory encoding or retrieval tasks, as described above using data from task-related functional neuroimaging experiments. This observation has led to the hypothesis that one activity that may be prominently occurring during these 'rest' epochs is thinking about the past or future, or 'mental time travel,' which engages episodic memory systems of the brain.

The convergence of thinking about functional brain systems and observations derived from studies of undirected 'rest' epochs of experiments has led to an explosion of studies using 'resting-state' functional connectivity MRI (fc-MRI), which is an exciting new neuroimaging technique for investigating large-scale functional-anatomic systems. Spontaneous fluctuations in BOLD signal can be readily detected in subjects whether or not a task is being performed. The degree to which these spontaneous fluctuations are correlated between different brain regions can be interrogated using a systems perspective. The initial experiments in this field have validated findings using this technique against findings using the same technique in anesthetized monkeys, and have demonstrated that functional brain networks identified using fc-MRI correspond to networks identified using traditional tract tracing methods (Vincent *et al*, 2007). These techniques have already been used to show the presence of a hippocampal–parietal network (Vincent *et al*, 2006), and the distinction between subnetworks within the MTL memory system, including the rostral hippocampal–perirhinal network *vs* the caudal hippocampal—parahippocampal–retrosplenial network (Kahn *et al*, 2008). This approach will clearly provide valuable novel contributions to knowledge about human memory networks in the brain, and will likely help provide further links between human and animal data. Figure 6 illustrates the spatial localization of these brain regions.

HUMAN MEMORY DISORDERS

A host of disorders can lead to amnesic syndromes in humans, including prominent deficits in episodic memory. Systematic studies of syndromes in which amnesia is the core symptom can provide valuable insights into the functional neuroanatomy and neuropsychology of human memory function. New insights into a few of these syndromes are highlighted here. Some neuropsychiatric disorders, including depression (Drevets *et al*, 2008 # 4760; Neumeister *et al*, 2005 # 4773), schizophrenia (Drevets *et al*, 2008; Neumeister *et al*, 2005), and posttraumatic stress disorder (Shin *et al*, 2004), seem to affect memory systems (particularly the MTL) in important ways but the core clinical phenotype involves affective-cognitive dysfunction beyond episodic memory, so they will not be reviewed here.

As many investigative groups tend to focus on one or a few of these disorders, the methods used to study these various forms of human amnesia have often been heterogeneous, hindering the development of generalizable conclusions across etiologies of amnesia. It would be beneficial for investigators to consider harmonizing, as best as possible, methods between human and animal studies, as well as between human cognitive neuroscience and patient-oriented neuropsychological studies of human amnesias of different etiologies.

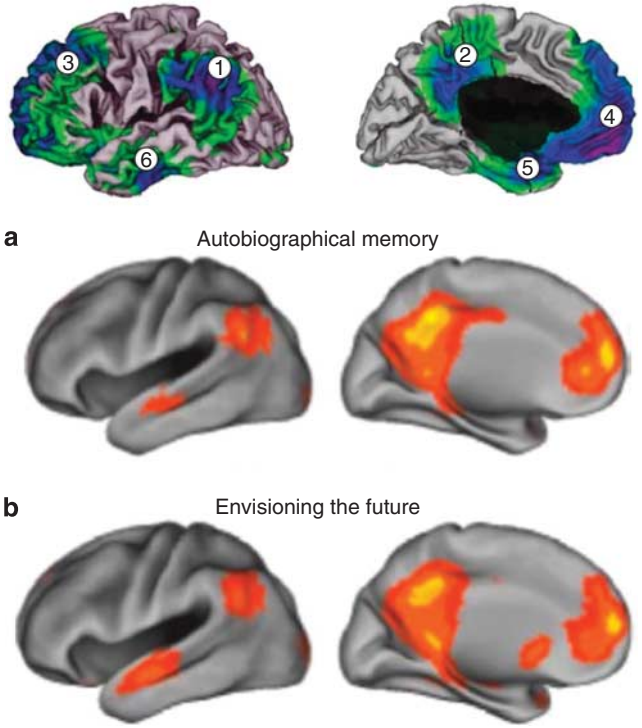

Figure 6. Cortical areas of the 'default mode' network, which is a set of brain regions that are deactivated below baseline level during the performance of most types of tasks (top, including inferolateral parietal (1), posterior cingulate/precuneus (2), dorsolateral prefrontal (3), medial prefrontal (4), medial temporal (5), and rostrolateral temporal (6)). These same regions are activated above baseline during the retrieval of autobiographical memories (a) and during the envisioning of specific potential future events (b).

Alzheimer's Disease

AD is the most common clinical amnesic syndrome, although it is important to keep in mind that by definition its diagnosis involves the presence of more than pure memory loss—the dementia of AD is a multidomain disorder, typically including executive dysfunction and varying degrees of visuospatial and language deficits. The prodromal phase of AD before dementia, which may last for a decade or more, is referred to as mild cognitive impairment (MCI), the prototypical form of which is amnesic. Amnesic MCI has received extensive investigative attention in the last decade (Frank and Petersen, 2008), with recent efforts illuminating functional and structural abnormalities in the MTL (Dickerson and Sperling, 2008).

The anatomy of AD not only involves prominent MTL pathology very early in the course of the disease (Gomez-Isla *et al*, 1996), but also pathologic involvement of lateral temporoparietal and medial parietal cortex, as well as a lesser (and more variable) degree of pathology in lateral and medial prefrontal cortex. Although the involvement of these non-MTL cortical regions has been long known from studies of postmortem tissue (Arnold *et al*, 1991; Tomlinson *et al*, 1970), their early involvement has been clarified with modern *in vivo* neuroimaging studies (Buckner *et al*, 2005; Dickerson *et al*, 2009; Klunk *et al*, 2004). Figure 7 shows MTL atrophy in a patient with mild AD.

Structural neuroimaging has shown the atrophy of regions within the MTL memory system in AD (Jack *et al*, 1997), as well as cortical regions that include important hubs of the episodic memory system (Dickerson and Sperling, 2008). Figure 8 highlights cortical regions that undergo atrophy in AD. The degree of atrophy of some of these regions relates to the level of specific types of memory impairment in AD (de Toledo-Morrell *et al*, 2000). Beyond structural measures of regional brain atrophy, functional neuroimaging has shown that dysfunction of these regions is present in patients with AD and that the level of dysfunction relates to the severity of memory impairment (Chetelat *et al*, 2003; De Santi *et al*, 2001; Mosconi *et al*, 2008). Recently, revolutionary new imaging technology using molecular ligands that bind to pathologic protein forms that accumulate in the AD brain is illuminating the localization and severity of pathology in various brain regions in living patients (Klunk *et al*, 2004; Small *et al*, 2006). Investigators have begun to combine these various imaging modalities to highlight the important observation that the molecular pathology of AD is localized in and is associated with dysfunction and atrophy of brain areas that include the episodic memory network (Buckner *et al*, 2005; Mormino *et al*, 2009). Further work using these techniques promises to build important bridges spanning the gap between postmortem histology and *in vivo* imaging measures of brain-behavior changes in patients with AD.

The memory deficit of AD is classically conceptualized as a dysfunction of consolidation or 'storage' (Salmon, 2008). This is widely measured in the clinic using tests of delayed free verbal recall, which show the patient's inability to spontaneously retrieve words that were encoded 10–20 min or so previously. Retention or 'savings' measures are also heavily used, which explicitly provide a measure indicting the percentage of information that was initially recalled during learning that is still able to be recalled without cueing after a delay. Other hallmarks of this amnesic syndrome include intrusions from interference materials and discriminability deficits on recognition measures.

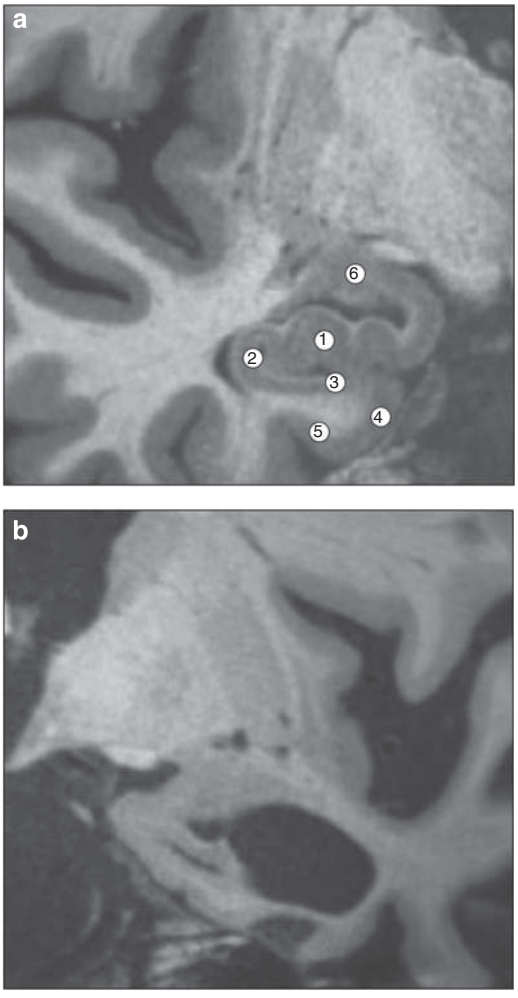

Figure 7. Ultrahigh-resolution (380 μm in-plane voxel size) structural MRI images of the human medial temporal lobe in a 24-year-old neurologically intact individual (a) and in a 72-year-old patient with mild Alzheimer's disease (b). In the young individual, a variety of MTL subregions can be seen, including CA3/dentate gyrus (1), CA1 (2), subiculum (3), entorhinal cortex (4), perirhinal cortex (5), and amygdala (6). Hippocampal formation and other medial temporal lobe structures are atrophic in Alzheimer patient.

It is important to recognize that delayed free recall of recently learned information is dependent on a variety of processes subserved by the large-scale memory network as outlined above, including executive control processes involved in retrieval effort and search as well as monitoring and decision making, which are likely subserved by systems outside the MTL, in addition to the primary memory processes supported by the MTL itself. It may be that this

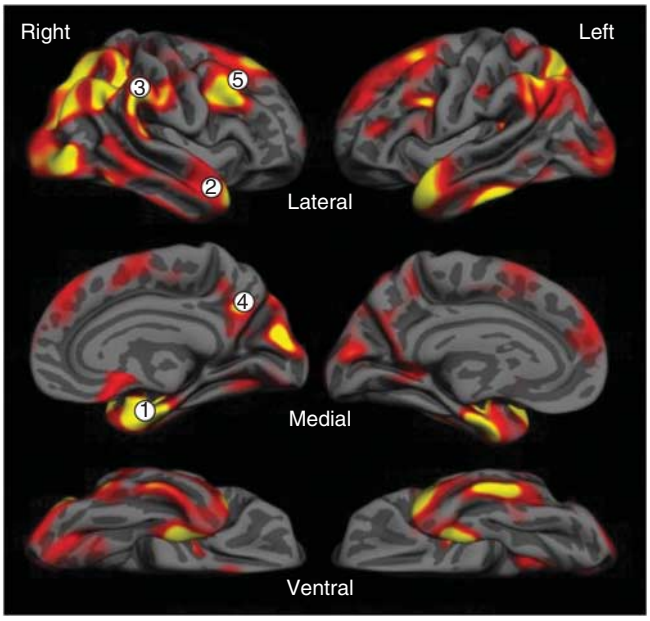

Figure 8. The cortical signature of regional thinning in Alzheimer's disease. Brain regions highlighted in red/yellow are thinner than age-matched cognitively intact controls in mild AD. The episodic memory network is prominently affected (including the medial temporal lobe (1), parts of the lateral parietal cortex (3), and posterior cingulate/precuneus (4)), as are nodes of several other networks (including the parts of the lateral parietal cortex (3), temporal pole (2), and dorsolateral prefrontal cortex (5)) subserving cognitive and behavioral function with relative sparing of sensorimotor regions.

form of memory test is sensitive to early AD because it draws on so many components of the system, yet this also makes it relatively nonspecific.

A number of recent investigations using methods drawn from cognitive neuroscience have highlighted other abnormalities of episodic memory performance in patients with AD. Studies of the dual process recollection and familiarity model initially suggested that familiarity was preserved in AD but recollection was not (Dalla Barba, 1997), but more recent investigations suggest that both processes may be impaired (Ally *et al*, 2009a). Regardless of their precise mechanisms, impairments in the ability to discriminate old from new, along from a more liberal response bias (Budson *et al*, 2006), seem to lead to an increase in false memory in AD (Budson *et al*, 2006). This may be one reason for the increased frequency of confabulation in AD (Attali *et al*, 2009).

Recent studies of prospective memory in AD suggest that there are prominent impairments in this form of memory, possibly even of greater severity than the retrospective deficit (Blanco-Campal *et al*, 2009).

Finally, the finding that the picture superiority effect (pictures of objects are better remembered than words representing the same objects) is preserved in AD (Ally *et al*, 2009b) highlights the fact that clinical approaches to memory assessment in AD often make little use of observations from basic cognitive neuroscience. That is, on verbal memory testing, which is the standard approach to testing that is widely used in AD clinical research and drug trials, patients with AD often reach floor performance, making it difficult to detect effects of interest, whereas if pictorial stimuli were used there might still be enough variance to enable the detection of effects of interest.

Hippocampal Sclerosis

Hippocampal sclerosis is a pathologic diagnosis involving neuronal loss and gliosis of the hippocampal formation, preferentially affecting the CA1 region and subiculum (Dickson *et al*, 1994; Lippa and Dickson, 2004). Although it has received relatively little investigation, it seems to be a relatively common pathologic finding in elderly patients with dementia, particularly in individuals greater than 80-years old. It is distinct from hippocampal or mesial temporal sclerosis associated with epilepsy. A recent community-based study of the neuropathology of amnesic MCI identified hippocampal sclerosis in 3 of 15 patients who died (Petersen *et al*, 2006). Detailed neuropathologic investigation of a series of 10 cases showed the presence of τ-positive lesions and the accompaniment of other non-Alzheimer pathologies, frequently a form of frontotemporal lobar degenerative pathology (Probst *et al*, 2007). The authors also reported frequent asymmetric hippocampal and ipsilateral mammillary body atrophy, which they proposed could be used as an imaging marker potentially helpful for diagnosis. Although there are currently relatively little data about hippocampal sclerosis as human amnesic syndrome and clinical diagnostic criteria have yet to be developed, it seems that the frequency and specificity of this etiology of late-life amnesia warrants further investigation.

Amnesias Associated with Focal Lesions

Focal lesions of hippocampal subregions (particularly CA1, Sommer's sector) and other portions of the MTL can be produced by hypoxic-ischemic injury (eg, because of cardiac arrest, asphyxiation, carbon monoxide poisoning), infectious processes (eg, herpes encephalitis, which often affects temporal isocortex as well as MTL), inflammatory processes (eg, forms of autoimmune limbic encephalitis), and other disorders. Ischemic stroke (particularly involving the posterior cerebral artery) can cause MTL damage, and can also affect other regions of the large-scale memory system, including thalamus; hemorrhagic stroke can affect basal forebrain and neighboring regions.

Developmental amnesia is a condition typically caused by perinatal hypoxic-ischemic injury, with resultant emergence of the memory deficit during development typically after the toddler years (Vargha-Khadem *et al*, 1997, 2001). In recent years, studies have begun to elucidate the normal development of recognition memory in first few days of infancy with recognition memory being present over longer delays as development progresses in the first year of life, followed by the development of semantic memory later in the first year of life, followed finally by the gradual

development and elaboration of forms of free recall, source memory, and flexible memory over the course of childhood (de Haan *et al*, 2006). This normal trajectory can be profoundly derailed as a result of a variety of rare disorders early in life. It seems that some individuals with primarily hippocampal developmental damage may be predominantly impaired in free recall and recollective aspects of recognition, with relative preservation of familiarity-based recognition memory (Baddeley *et al*, 2001; Brandt *et al*, 2008). Furthermore, semantic memory can be partially or even quite well preserved, including the acquisition of new semantic knowledge (Gardiner *et al*, 2008). Although neuroimaging data indicate that structures outside the MTL can be damaged in hypoxic-ischemic amnesia, including regions of the thalamus, cases of developmental amnesia that have been studied in detail are associated with at least 20–30% volume loss bilaterally (Isaacs *et al*, 2003).

A body of cognitive neuroscience research with focal MTL lesion patients has centered on the hotly debated issues regarding dual process theories of memory and, for proponents of such models, the relative importance of the hippocampal formation as opposed to medial temporal cortex for recollection *vs* familiarity (Aggleton and Brown, 1999; Eichenbaum *et al*, 1994). Evidence exists in support of the contention that patients with damage thought to be fairly restricted to the hippocampal formation have memory deficits predominantly involving recollection with relative sparing of familiarity, whereas those with larger lesions including MTL cortex have both recollection and familiarity deficits (Eichenbaum *et al*, 2007). However, there are many contentious issues in this debate (Squire *et al*, 2004), one of the most important of which is that it is very difficult to be confident in our knowledge of the precise localization of the lesions *in vivo*.

Going back to studies with HM, there has been debate about the degree to which the acquisition of new semantic information can be performed in patients with MTL lesions. This is of interest in part because of questions regarding whether facts (semantic memory) are initially learned in a manner similar to events (episodic memory). Recent studies of patients with MTL lesions continue to provide evidence that it is possible for humans with significant MTL damage to learn some new facts, albeit with significant difficulty (Bayley *et al*, 2008).

Retrograde amnesia has received increasing attention recently, with a growing number of debates emerging about the types, relative severity (particularly in relation to anterograde amnesia), and temporal gradient of remote memory impairment (Kopelman and Kapur, 2001; Squire and Bayley, 2007). More sophisticated methods for testing the challenging domain of autobiographical memory in patients with focal amnesias have demonstrated intact remote memory in patients with damage restricted to hippocampal formation (Kirwan *et al*, 2008). Creative single-case studies, including a behavioral and functional MRI study of a patient with apparent isolated retrograde amnesia (Levine *et al*, 2009), have begun to suggest that dysfunction in medial prefrontal and parietal cortical regions impedes the first person re-experiencing of past events.

Although investigations are increasingly being performed of patients with amnesic syndromes characterized and localized primarily on the basis of neuroimaging data, it is extremely important to continue to perform postmortem examinations of as many of these individuals as possible. The neuropathology of a handful of patients who have been studied in detail during life has been described, supporting the notion that focal hippocampal pathology can result in a dense anterograde as well as graded retrograde amnesia (Rempel-Clower *et al*, 1996; Zola-Morgan *et al*, 1986). A recent series shows similar amnesic syndromes in a patient with focal hippocampal pathology as well as two patients with thalamic pathology (one with infarcts and one with Korsakoff's syndrome), which the authors interpret to indicate that damage to the MTL or diencephalic memory system (including dorsomedial nucleus, adjacent internal medullary lamina, mammilary bodies, mammilothalamic tract, or anterior nuclei) can produce similar memory disorders (Gold and Squire, 2006).

The thalamic components of the episodic memory system are receiving increasing attention in functional neuroanatomic studies as well as behavioral investigations (Van der Werf *et al*, 2003). A detailed report including imaging (DWI tractography of white matter and anatomical imaging of gray matter) of thalamic nuclei and mammilothalamic tracts indicated that, although the two patients in the report exhibited anterograde amnesia, their performance did not fit as well as predicted with the roles of thalamic components of the system in the dual process model of recognition memory (Cipolotti *et al*, 2008).

Although the role of the prefrontal cortex in confabulation has been hypothesized on the basis of single case or small group studies (Benson *et al*, 1996), there have been only a few investigations of large samples of patients with prefrontal lesions. Confabulation, defined as a 'false' memory that the patient believes to be true, often involving a statement about a personal autobiographical event that the patient never in fact experienced, has been thought to result from a memory deficit with superimposed executive dysfunction that leads to impairment in monitoring. A recent investigation of 38 patients with frontal lesions and 12 patients with temporoparietal lesions indicated that confabulation was strongly associated with orbital and medial prefrontal (particularly anterior cingulate) lesions (Turner *et al*, 2008). As some patients with confabulation did not show executive deficits, the authors interpret their data to indicate that confabulation may be a result of a specific executive deficit not tapped by traditional tests or of a specific episodic memory monitoring or control deficit localized to ventromedial prefrontal cortex.

Episodic memory performance in patients with focal parietal lesions has received very little attention. An initial study of source memory in patients with lateral parietal lesions indicated that no impairment was present in these

patients (Simons *et al*, 2008). Although an fMRI experiment had been used in this study to localize the posterolateral parietal activation associated with a source memory judgment and the patients' lesions included this area, the authors ended by concluding that lateral parietal cortex may participate in—but does not seem to be necessary for—this form of recollection.

Epilepsy

It has long been appreciated that many patients with epilepsy (and seizure disorders more generally) exhibit memory impairment. This is particularly true among patients with temporal lobe epilepsy (TLE), the most common form of adult-onset epilepsy, in which epileptiform activity commonly originates in or involves the hippocampal formation and neighboring MTL cortical regions. Starting with the pioneering work by Milner and colleagues at the Montreal Neurological Institute, neuropsychological performance data have suggested a material-specific memory disorder in patients with TLE, which is thought to typically begin as a lateralized disorder that produces verbal memory impairment when localized to the dominant hemisphere and visual or visuospatial memory impairment when localized to the nondominant hemisphere (Milner, 1972).

Recent investigations motivated in part by astute clinical observations indicate that there are other forms of amnesic disorders in patients with epilepsy. Transient epileptic amnesia (TEA) (Kapur, 1993) is a form of anterograde and/or retrograde amnesia that occurs as brief, usually recurrent, episodes often in middle-aged or elderly patients with epilepsy. The pathophysiology of the disorder is thought to involve an ictal or postictal form of epileptic MTL disturbance. In addition to these brief episodic periods of amnesia, TEA may also be accompanied by two other forms of persistent memory loss: accelerated long-term forgetting and remote memory impairment (Bell and Giovagnoli, 2007; Butler *et al*, 2007). Accelerated long-term forgetting describes the apparent normal initial learning and recall of information over minutes to hours followed by an unusually rapid loss of information over days to weeks (original ref). Remote memory impairment involves the relatively prominent impairment of remote autobiographical or semantic memory compared with performance on tests of recent memory (Kapur *et al*, 1989). Both of these latter forms of memory impairment have been reported in single case or small group studies, but generally have not been very heavily investigated.

Further studies of these forms of epileptic amnesia will likely illuminate important outstanding questions in the field of human memory disorders. TEA often occurs in individuals of similar age to those that experience transient global amnesia (TGA), although the duration of the episode of amnesia is usually shorter in TEA (30–60 min) than in TGA (4–10 h). A better understanding of these disorders could provide insights into the vulnerability of the normal dynamics of MTL function, and may also provide opportunities for the investigation of the behavioral effects of transient amnesia, as experimental methods to transiently inactivate (eg, transcranial magnetic stimulation) MTL have proven elusive to date. As TEA has been commonly reported to occur on awakening, further studies may shed additional light on the interactions between sleep and memory (Stickgold and Walker, 2007). Finally, accelerated long-term forgetting and remote memory impairment will likely provide valuable information relevant to theories of memory consolidation (Alvarez and Squire, 1994; Moscovitch and Nadel, 1998).

Transient Global Amnesia

TGA is a striking clinical syndrome involving the acute onset of anterograde and temporally graded retrograde amnesia with otherwise normal neuropsychiatric function (Fisher and Adams, 1964; Hodges and Warlow, 1990). It usually lasts less than 1 day and resolves completely, except for the loss of memory for experience during the episode. A wide range of pathophysiologic mechanisms have been postulated, including migraine pathophysiology (spreading neurophysiologic depression), ischemia, epileptiform activity, and others (Sander and Sander, 2005).

Several recent findings have led to the revision of pathophysiologic hypotheses. Observations that patients are often engaged in stressful or physically vigorous activities before TGA led Lewis (1998) to propose that the combination of a valsalva-inducing process in combination with jugular venous insufficiency would lead to a state of venous stasis that may preferentially affect the MTL. Although this proposal is controversial, there is a substantially higher rate of jugular venous insufficiency in TGA patients than in controls (Sander and Sander, 2005). The apparent presence of phobic personality traits in many TGA patients (Inzitari *et al*, 1997) has led to the suggestion that hyperventilation may predispose to cerebral vasoconstriction and hypoperfusion (Pantoni *et al*, 2000).

Advances in diffusion-weighted MRI have enabled the detection of punctate lesions with restricted diffusion in some patients with TGA, which usually (but not always) indicates ischemia. In a recent study that used DWI, a large majority of patients were found to have DWI abnormalities in the hippocampal formation, usually unilaterally but in some cases bilaterally (Sedlaczek *et al*, 2004). The authors proposed that the vascular anatomy of the hippocampal formation, with the dorsolateral aspect being a watershed zone, may predispose to the vulnerability of regions in which the lesions were frequently detected, and that more sensitive imaging methods may enable the more routine detection of such subtle abnormalities.

CONCLUSIONS AND FUTURE DIRECTIONS

This review suggests several areas of convergence in studies on the anatomy of the MTL memory system and

the larger-scale distributed memory system including brain regions outside the MTL, as well as neuropsychological and neurophysiological studies on episodic memory function in animals and humans. First, there is growing convergence of evidence that the hippocampus serves a fundamental and selective role in episodic memory across mammalian species. In animals, experimental lesions restricted to the hippocampus result in relatively selective loss of features of episodic memory. Similarly, studies on memory disorders in humans show that compromise of hippocampal function across a broad variety of disorders results in deficits in episodic memory with variable sparing of other aspects of declarative memory. Harmonization of behavioral and anatomic methods within and across species, to the degree possible, should provide further evidence of the specificity of hippocampal lesions on forms of episodic memory and related abilities. Second, and correspondingly, physiological studies, involving single neurons recordings in animals and functional imaging studies in humans, support the view that the hippocampus is involved in episodic memory, and may be particularly involved in encoding conjunctions of important events with where and when they occur. Third, additional studies have shown the cortical areas adjacent to the hippocampus (perhirhinal, parahippocampal, and entorhinal cortex) also have a function in episodic memory across species. Additional work on the detailed anatomy and connectivity of MTL regions, behavioral paradigms, and important technical advances in neurophysiology and functional neuroimaging data acquisition and analysis will likely contribute in valuable ways toward our understanding of the functional neuroanatomy of this system. Finally, substantial evidence from studies on humans, and some evidence on animals, show a large-scale distributed network of cortical areas that participate in important ways in episodic memory; particularly, the prefrontal cortex in humans and animals has a critical function in executive functions that monitor and manage episodic memory. Further studies in multiple animal species as well as in humans will shed light on the fundamental roles of these brain regions and the ways in which humans differ from even our closest primate relatives.

There are also two major areas in which information is sparse, and future studies could elucidate how the episodic memory system works and how its disorders might be better understood and, hopefully, ameliorated. First, further work is needed to identify the distinct roles of anatomical components of the cortical–hippocampal system, including both the isocortical areas that are directly connected with the MTL and the allocortical and periallocortical areas immediately surrounding and intimately connected with the hippocampus. In addition to further characterizing their individual roles, we need to understand how these areas interact with each other in support of the encoding, organizing, and retrieval of episodic memories. Studies in both animals and humans, which involve simultaneous monitoring of different components of this system, using multiple single recordings in animals and functional connectivity analyses in humans, may show how the system components normally interact and how the system processing breaks down in memory disorders. Second, we need to understand how the detailed circuitry within subdivisions of the hippocampal formation—that is, Ammon's horn, the dentate gyrus, and subiculum, and also the circuitry along the rostrocaudal axis of the hippocampus—supports computations that underlie features of episodic memory. For example, the findings that describe the marked attractor dynamics (pattern completion and pattern separation) of area CA3 and the dentate gyrus in both animals and humans may provide a window in the computational circuitry on which features of episodic memory are based, and those computations might be the functions that are fundamentally compromised in memory disorders (for reviews, see Colgin *et al*, 2008; Guzowski *et al*, 2004). Similarly, understanding how potentially distinctive representations along the rostrocaudal axis of the hippocampus are integrated might provide clues about a functional topography in this system. Greater understanding of functional neuroanatomy and computational processing of episodic memory systems, and how they can be modulated pharmacologically, should pave the way toward new treatments for memory disorders.

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DISCLOSURE

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