Current Topics Regarding the Function of the Medial Temporal Lobe Memory System

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Abstract The first clear insight that the medial temporal lobe of the human brain was in fact a system of anatomically connected structures that were organized into a memory system came in 1957 from the observations by Brenda Milner of the noted amnesic patient H.M. Subsequent work in humans, monkeys, and rodents has identified all of the components of the medial temporal lobe (MTL) that formed the memory system. Currently, work is ongoing to identify the specific contributions each structure in the medial temporal lobe makes towards the formation and storage of long-term declarative memory. The historical background of this work is described including what insights the study of noted neurologic patients H.M. and E.P. provided for understanding the function of the medial temporal lobe. The development of an animal model of medial temporal lobe function is described. Additionally, the insights that lead to the understanding that the brain contains multiple, anatomically discrete, memory systems are described. Finally, three current topics of debate are addressed: First, does the perirhinal cortex exclusively support memory, or does it support both memory and higher order visual perception? Second, is there an anatomical separation between recollection and familiarity? Third, is the organization of spatial memory different between humans and rats, or perhaps the difference is between the working memory capacities of the two species?

Keywords Working memory · Perirhinal · Recollection · Familiarity
Spatial memory · H.M. · E.P.

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1 Introduction

This first clear insight that the medial temporal lobe (MTL) of the human brain was in fact a system of anatomically connected structures that were organized into a memory system came in 1957 from the observations by Brenda Milner of the noted amnesic patient H.M. Subsequent work in humans, monkeys, and rodents has identified all of the components of the medial temporal lobe that formed the memory system. Currently, work is ongoing to identify the specific contributions each structure in the medial temporal lobe makes towards the formation and storage of long-term declarative memory.

2 Background

2.1 Neurologic Patient H.M

As early as 1899, there was some indication that the hippocampus might be important for memory function. At a medical meeting in St. Petersburg, von Bekhterev (1900) displayed the brain of a patient who had exhibited profound memory problems as the most prominent clinical symptom. The primary brain pathology was described as being a bilateral softening of the hippocampus and medial temporal cortex. During the ensuing decades, a few clinical case studies also suggested a relationship between memory impairment and damage to structures of the medial temporal lobe (Glees and Griffith 1952; Grünthal 1947; Hegglin 1953). However, a clear relationship between memory ability and medial temporal lobe function had to await the clinical descriptions provided by Brenda Milner of the

amnesic patient Henry G. Molaison, known now in the scientific literature as patient H.M. (Scoville and Milner 1957).

H.M. had an extensive history of minor and major seizures that were unresponsive to standard antiepileptic medication. He had minor seizures beginning at 10 years of age, and major seizures began to appear when he was 16. The major seizures occurred without warning as generalized convulsions that involved loss of consciousness followed by prolonged periods of sleep. Despite high, near-toxic, doses of medication, the major attacks increased in severity and frequency until eventually, he was unable to work or lead a normal life. A decision was then made with the consent of the family to attempt to relieve the seizures through an experimental surgical intervention. On September 1, 1953 at Hartford Hospital in Hartford Connecticut, William Scoville removed H.M.'s medial temporal lobes bilaterally. The surgery involved tissue removal through a supra-orbital trephine with a fine suction tube and attached cautery while the frontal lobe was carefully retracted. The lesion was designed to extend posteriorly for a distance of 8 cm from the tips of the temporal lobes, with the temporal horns constituting the lateral edges of resection.

The surgery was successful in as much as it reduced the frequency and severity of the seizures. However, H.M. was left with profound amnesia. It is notable that although a number of patients had undergone similar removals prior to H.M., those surgeries were performed in an attempt to relieve severe psychosis rather than to relieve seizures. Because the psychosis remained severe in those patients following surgery, the memory problems that must have surely resulted from the medial temporal lobe resection were not appreciated. For H.M. however, the devastating memory impairment was obvious as soon as he had recovered from surgery (Scoville 1954).

2.1.1 The Anatomy of H.M.'s Lesion

Subsequent standard MRI scans (Corkin et al. 1997), in situ MRI scans (Augustinack et al. 2014) and direct histological analysis (Annese et al. 2014) showed that the lesion was bilaterally symmetrical and included the medial temporal polar cortex, piriform cortex, essentially all of the entorhinal cortex (1–2% sparing) most of the perirhinal cortex and subiculum and amygdaloid complex. The anterior half of the intraventricular aspect of the hippocampal formation was removed. This included the dentate gyrus, hippocampus, and subicular complex. The portion of the hippocampus that was spared was the most posterior aspect where the hippocampus ascends in a dorsoposterior direction. The right hippocampus had slightly more preserved tissue than the left (preserved hippocampus was 45.4 mm in the left hemisphere and 47.2 mm in the right; Annese et al. 2014). It was also notable that while the general size and cortical folds of the cerebral hemispheres were unremarkable for an individual of H.M.'s age, white matter lesions that would be consistent with infarctions were observed. Some cerebellar shrinkage was also apparent and this was probably due to the prolonged exposure to phenytoin sodium, which was administered as part of H.M.'s seizure

management. There was also a small focal lesion in the left lateral orbital gyrus and involved both cortex and underlying white matter (Annese et al. 2014).

2.2 *Neurologic Patient E.P*

In November of 1992, when E.P. was 70 years old he became sick with flu-like symptoms that included a fever and lethargy. It was at this point that he also experienced a distinct loss of memory. Over the next several days, the memory problem became worse until he was eventually hospitalized. There he was diagnosed with a viral infection and immediately provided with an antiviral medication for 10 days. Two weeks after admission, a T2-weighted MRI scan revealed that the infection and brain swelling had produced viral encephalitis that was bilateral and symmetrical and encompassed the medial temporal lobe. EP successfully recovered from the infection but the brain damage and associated memory impairment was permanent.

2.2.1 The Anatomy of E.P.'s Lesion

Almost all of the hippocampal formation was removed bilaterally including the cell fields of the dentate gyrus, CA1, CA2, CA3, CA4, and the parasubiculum, presubiculum, and subiculum. Only isolated islands of cells remained in the most causal levels of the hippocampal formation. The amygdala was completely removed bilaterally. Neocortical areas were also bilaterally damaged and this damage was symmetrical. The entorhinal cortex was essentially removed bilaterally with only the layer II cell islands observable at the extreme posterior extent of the structure. The entire perirhinal cortex was ablated bilaterally. Finally, the parahippocampal cortex was mostly present with approximately 25% total damage along the anteroposterior extent. It was notable however that the clear laminar organization of healthy neocortical tissue was ill defined in E.P.'s spared parahippocampal cortical tissue. Damage outside of the medial temporal lobe: The rostral fusiform gyrus was substantially damaged. There was also notable damage to the medial mammillary nucleus, medial septal nucleus, and the claustrum as well as more limited, punctate cell loss in the anterior nucleus of the thalamus and pulvinar. Most of the additional abnormalities involved gliosis in the white matter of the temporal stem (Insausti et al. 2013).

2.3 *Insights About the Organization of Memory from H.M. and E.P*

After his surgery, H.M. essentially became a professional research subject and was studied for a full half-century by Milner, her student Suzanne Corkin, and their

various colleagues. He died at the age of 82 on December 2, 2008. It is generally accepted that the evaluations of H.M. initiated the modern era of memory research (Squire 2009). Following his recovery from viral encephalitis, Larry Squire and his colleagues studied E.P. for 14 years beginning in 1994. E.P. died at the age of 84 on March 3, 2008. Although the etiologies of the H.M.'s and E.P.'s brain damage were completely different, the final result was a large bilateral lesion of the medial temporal lobe. H.M.'s lesion more restricted to the MTL that was E.P.'s, but E.P.'s MTL damage more was complete. Nonetheless, the similarity of the damage and the rigor and extent to which these two men were evaluated following their brain damage allowed at least four fundamental principles regarding the organization of memory to be illuminated.

2.3.1 Memory Is a Distinct Cerebral Ability

Before H.M., the idea that memory function was a distinct ability, separable from other functions like intelligence, perception, motivation, or personality was not well accepted. This was due in large part to the systematic and influential work of Karl Lashley. Lashley's work was designed to determine if memory could be localized by making discrete and systematically varied brain lesions in rodents and monkeys and other animals and then testing memory acquisition and retention (Lashley 1929). The conclusion was that memory was not localized but rather was distributed throughout the cortex (termed mass action) and that different parts of the cortex were capable of forming memories when other parts were damaged (termed equipotentiality). Work with H.M. and later E.P. demonstrated that their dramatic memory impairment occurred against a background of preserved intelligence, working memory, personality, perceptual ability, and motivation. The primary impairment was exclusively an impairment of long-term memory. This showed that memory was indeed a discrete brain function and this function was localized to the MTL. The reasons for the discord between Lashley's work and the findings from H. M. and E.P. are discussed below in the section on the development of an animal model of MTL amnesia.

2.3.2 The MTL is Not the Repository of Permanent Long-Term Memory

MTL damage produces an impaired ability to form new memories (anterograde amnesia) and an impaired ability to retrieve some older memories that were acquired before the brain damage (retrograde amnesia). Importantly, the impaired ability to retrieve memories acquired before the brain damage does not extend equally to all memories. Rather, memories that were acquired a short time before the brain damage are disproportionally impaired relative to older memories. That is, while more recent memories appeared to be completely lost, older memories, from say childhood, appeared to be completely normal. This phenomenon is often

described as a temporally graded retrograde amnesia (TGRA). These observations had two profound implications to understanding the organization of memory. The first implication is that while the MTL is essential for memory encoding and retrieval, it is not the ultimate repository for permanent long-term memory. The second implication is that when memories are first acquired, they are not stored in a form that will persist as memory indefinitely. Rather these memory representations apparently undergo a process of reorganization that transforms them from MTL-dependent memory into MTL-independent memory. This process is referred to as systems consolidation.

2.3.3 MTL Damage Does Not Impair Working Memory

MTL damage does not prevent the acquisition of limited amounts of information that can be held "in-mind" for brief periods of time. This ability can be described a short-term memory, but more formally as working memory or immediate memory. This is the type of memory that allows us to remember, for example, a phone number long enough to dial it before it is forgotten. This information can be maintained for longer periods of time if it is mentally rehearsed, but when distracted, the information is immediately lost. It is also the type of memory that allows a patient with MTL damage to remember a posed question long enough to comprehend the meaning of the question and to provide a suitable answer. Normally, information contained within working memory can be encoded into long-term memory through focused attention or rehearsal, but with MTL damage this information cannot be encoded into LTM and will be quickly and permanently lost (e.g., Baddeley 2003).

2.3.4 MTL Damage Does Not Impair Many Other Forms of Memory

Despite the pervasive and debilitating memory impairment that follows MTL damage, other forms of memory are spared. The first clear indication of this dissociation came when it was discovered that H.M. was able to learn a mirror drawing skill as well as healthy subjects (Milner 1962). In this task, subjects learn to use a pencil to trace between lines viewed through a mirror. At first, this is difficult because each correct movement must be made in the opposite direction from what is normally required. With practice, subjects steadily improve this skill. H.M. improved at the same rate as healthy subjects despite the fact that after the test he had no memory of even attempting the task. Similarly, E.P. exhibited normal differential delay eyeblink classical conditioning despite not remembering the conditioning session or any of the associated pieces of experimental equipment (Clark and Squire 1998). Because these examples represent an experience-based change in behavior, they could correctly be termed "memory," and thus forms of memory that are independent of the MTL. What gradually became clear was that there are many different forms of memory that depend on different brain systems

and operate using different neural computations to accomplish memory (see Multiple Memory Systems below).

2.3.5 MTL Function Supports Declarative Memory

Declarative memory is the type of information that is available to conscious awareness of the memory content. It is what one ordinarily means when talking about memory. In other words, it is memory in the colloquial form. For example, you have a memory for what the word "breakfast" means and you presumably have a memory for what you had for breakfast this morning. This type of memory was termed declarative memory precisely because it could be brought to mind and declared (Squire and Zola 1996). Further, there are two primary forms of declarative memory known as semantic and episodic memory. The example above illustrates both types. Semantic memory describes the general bits of knowledge that have been acquired over a lifetime. This knowledge structure would include things like what different concepts mean. It would also include ideas and facts like what the word "breakfast" means. Episodic memory refers to the memory of autobiographical episodes (i.e., events) and could include all of the rich details that were present at the time of the specific event including what happened, the time and place it happened, and other associated emotions or contextual details including what one might have had for their most recent breakfast. This is the type of memory that allows one to reconstruct their past and by mentally traveling back in time to reexperience the event or episode. Recognition memory is a subcategory of declarative memory and simply refers to the ability to recognize anything that has been previously encountered. Two processes, recollection and familiarity (Atkinson and Juola 1974; Mandler 1980), are thought to support recognition memory. Recollection involves remembering specific details or other contextual information concerning a previously experienced episode. Familiarity simply involves knowing that an object (or anything else) was encountered previously, without having available any additional knowledge concerning the actual event or episode during which the information was acquired. Experimentally, these two processes have been studied using the "remember-know" paradigm where "remember" is a proxy for recollection and "know" is a proxy for familiarity and the possible anatomical distinction between these two processes is a current topic of investigation and is discussed further below.

2.4 Animal Model of Medial Temporal Lobe (MTL) Amnesia

Because early efforts to replicate H.M.'s memory deficit in animals were unsuccessful, there was some skepticism concerning the nature of the actual deficit. Work to establish an animal model began almost immediately when Scoville himself

came to Montreal and performed the identical surgery in monkeys that he had done with H.M. (Correll and Scoville 1965). Surprisingly (at the time), these monkeys and others with medial temporal lesions were able to learn tasks that appeared similar to memory tests that H.M. could not perform. For example, H.M. could not succeed on a delayed paired comparison technique that consisted of presenting two visual stimuli in succession, separated by a short time interval (Milner 1972). This observation and others implied that the delay between stimulus presentations was critical for observing memory impairment. However, monkeys with MTL lesions performed normally on visual discrimination problems designed to model the tests presented to H.M. (Orbach et al. 1960). This result persisted even when long delays and distractions were introduced (Orbach et al. 1960). The problem was that at the time, it was not understood that humans and experimental animals often approach seemingly similar tasks using different strategies that involve different memory systems. An important example is that monkeys tend to learn visual discriminations gradually over dozens of trials in a form of habit learning. Habit learning is independent of the MTL and supported by the basal ganglia (Mishkin et al. 1984; Teng et al. 2000). Thus, most of the tasks given to animals with hippocampal lesions were in reality skill-based tasks that patients with MTL damage would have been able to acquire, or they were tasks that animals would learn as a skill whereas humans tended to learn the task by consciously memorizing the material. Accordingly, establishing an animal model would require developing tasks that assess the type of memory impaired in amnesia.

The critical advance in forming a model of human medial temporal lobe amnesia was the establishment of one-trial memory tests for the monkey that assess declarative memory. Importantly, if one wants to relate the animal work to work in humans it is not sufficient to use any convenient test in which the animal must use memory. Instead, one must use "specifically designed animal analogs of those tests that do reveal impairment in human amnesiacs." (Gaffan 1974; p. 1101). In 1978, Mortimer Mishkin trained monkeys on the delayed nonmatching-to-sample (DNMS) task (Mishkin 1978). Here, monkeys were first presented with a sample object and then a choice of that sample object or a new object. The monkey received a reward by selecting the new object. This task exploited the monkey's natural tendency to select the novel object, which meant that animals learned this task quickly (Mishkin and Delacour 1975; Mishkin 1978). After training, the monkeys were prepared with lesions designed to mimic the damage sustained by H. M. Postoperatively the animals reacquired the nonmatching rule, and then the delay between the sample and choice phase was increased progressively from 10 s to 30, 60 and 120 s. In this study, the lesions produced a clear deficit, particularly at the longer delays. The demonstration of delay-dependent impairments was critical for at least two reasons. First, it reproduces the memory impairment phenotype seen in humans (intact working memory and impaired long-term memory). Second, when a brain lesion spares performance at short delays (when the demand on memory is small) and impairs performance selectively at longer delays (when the demand on memory is larger), it rules out a variety of alternative explanations for the impairment (e.g., including the ability to perceptually recognize objects,

motivational changes, stress responses, circadian influences, and secondary effects of the lesion including hyperactivity, increased distractibility, motor impairments, and other nonspecific effects).

This study and subsequent studies, which relied especially on the trial unique DNMS task (Zola-Morgan and Squire 1985; Mishkin 1982), document the successful establishment of an animal model of human medial temporal lobe amnesia in the monkey. These findings, and others, led to the conclusion that the hippocampal formation (the CA fields of the hippocampus, the dentate gyrus, the subiculum, and the entorhinal cortex) and the adjacent parahippocampal and perirhinal cortices comprise the major components of the medial temporal lobe memory system (Squire and Zola-Morgan 1991). Large lesions of this system in the monkey produce a pattern of memory impairment that closely resembles the phenotype when similar lesions occur in patients (e.g., patient H.M.; Scoville and Milner 1957; Corkin 1984; Corkin et al. 1997 and patient E.P.; Stefanacci et al. 2000). Subsequent work using the animal model characterized the memory impairment that followed damage to MTL structures. The impairment in monkeys with such lesions exhibits normal skill-based memory and normal habit-like memory (Malamut et al. 1984; Zola-Morgan and Squire 1984) as well as intact short-term memory (Overman et al. 1990). Finally, the impairments in monkeys are long-lasting (Zola-Morgan and Squire 1985) and multimodal (Murray and Mishkin 1984; Suzuki et al. 1993). A detailed description of the contributions of the rodent model is too extensive to be described here, but for review see (Clark and Martin 2005; Martin and Clark 2007).

2.5 Multiple Memory Systems

As early as the 1890s, the idea existed that memory was not a unitary ability. William James, in his classic book Principles of Psychology (1890), wrote separate chapters for describing memory and learned habits. Since then, theories of memory have usually distinguished two forms of memory, one form describing memory in the typical colloquial sense of the word and the other form describing motor memory. For example, theories distinguished between explicit and implicit memory (McDougall 1923), "knowing that" and "knowing how" (Ryle 1949), and declarative and procedural memory (Winograd 1975). The first biological insights into these distinctions came from the study of patient H.M. (Scoville and Milner 1957). H.M. had a profound impairment in declarative memory (memory for facts and events), but nonetheless could learn a motor skill (mirror drawing) as efficiently as controls, while retaining no memory of having practiced the task (Milner 1962). This finding indicated that memory is not a unitary ability. At the time of this finding, the preserved memory ability was thought to be restricted to motor skills, a less cognitive form of memory, while all other memory was still viewed as a single entity. However, we now understand that motor skills were not merely an exception, but rather were the first example of a range of memory abilities that depend on

brain systems other than the medial temporal lobe. Subsequent work identified other forms of experience-dependent behaviors that were independent of the medial temporal lobe and conscious awareness. Work in humans identified the phenomenon of priming, which is the improved ability to produce, detect, or classify an item due to a recent encounter with the same or related item (Tulving and Schacter 1990). In addition, the basal ganglia was found to be important for gradual, feedback-guided learning that forms the basis of habit memory (Mishkin et al. 1984; Packard et al. 1989). These tasks must be structured in a way that discourages attempts at memorization (for example, when outcomes of trials are determined probabilistically). In rodents, many discrimination tasks or tasks that require a particular response to be acquired are forms of habit memory and dependent on the basal ganglia (e.g., McDonald and White 1993). Simple forms of classical conditioning (Pavlov 1927), like delay eyeblink classical conditioning, were found to be dependent on the cerebellum and associated brainstem circuitry (Christian and Thompson 2003; Clark et al. 1992; Clark and Lavond 1993, 1994). Classical conditioning of fear responses is critically dependent on the amygdala which is

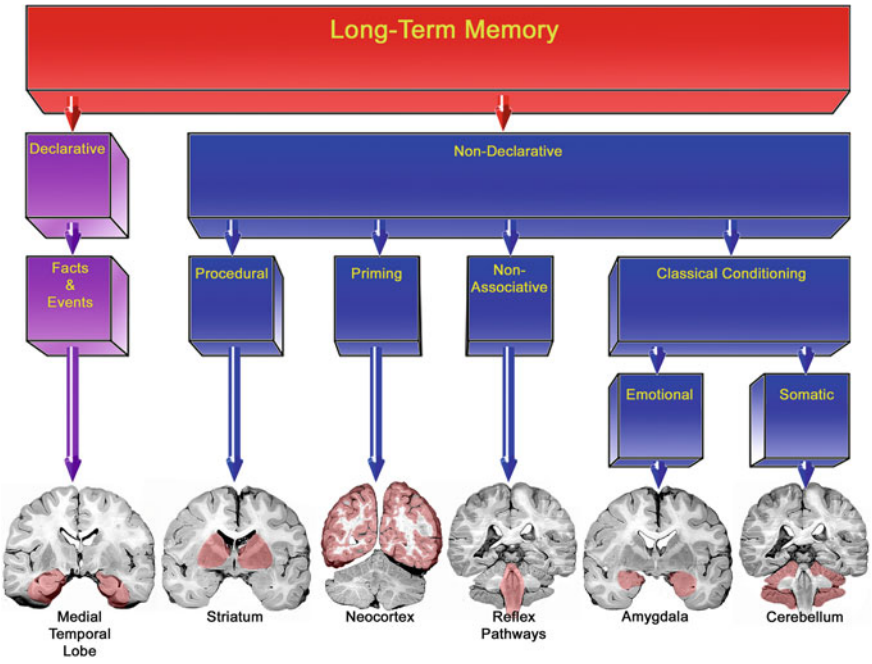

Fig. 1 Memory taxonomy. Long-term memory (purple box) is made up of declarative memory, which includes memory for facts and events (red boxes) and depends on the function of medial temporal lobe (MTL) regions. Nondeclarative memory (blue boxes) is an umbrella term encompassing a collection of learning and memory abilities that are independent the MTL and are principally supported by anatomically distinct and functionally independent brain regions. The critical brain region for each memory system is highlighted in red in coronal sections through the human brain. Adapted from Squire (1992)

thought to be the structure that permanently encodes and stores the hedonic value of the aversive stimulus (Fanselow and Gale 2003). Finally, phylogenetically early forms of behavioral plasticity like habituation and sensitization are also forms of nondeclarative memory. Figure 1 illustrates the categorical taxonomic organization of the mammalian long-term memory systems and the brain structures that support those systems.

2.6 The Organization of the Medial Temporal Lobe Memory System

The system of structures important for declarative memory includes the hippocampus (dentate gyrus, CA fields and subiculum) and the entorhinal, perirhinal, and parahippocampal cortices (Fig. 2; note that in the rat, the region that is synonymous with the parahippocampal cortex is referred to as postrhinal cortex because it is located posterior to the rhinal sulcus). The hippocampus can be conceptualized as residing at the end of a processing hierarchy located in the medial temporal lobe. The hippocampus receives inputs from both the perirhinal and parahippocampal cortices as well as the entorhinal cortex. Guided by the anatomy and physiology, it seems likely that the hippocampus extends and combines functions performed by the structures that project to it (Squire et al. 2007). Additionally, anatomical connections from different regions of neocortex enter the medial temporal lobe at different points. Thus, the higher visual areas TE and TEO project preferentially to the perirhinal cortex. Conversely, spatial information arrives in the medial temporal lobe via the parietal cortex and synapses exclusively in the parahippocampal cortex. Accordingly, it appears that object and spatial information remain segregated in the MTL until combined in the hippocampus (Fig. 3). Consistent with these anatomical facts, damage to parahippocampal cortex was found to impair spatial memory more did than damage to perirhinal cortex (Parkinson et al. 1988; Malkova and Mishkin 1997), and damage to perirhinal cortex impaired performance on the visual object DNMS task more than did damage to parahippocampal cortex (Ramus et al. 1994).

The perirhinal cortex and area TE are immediately adjacent to each other in the temporal lobe and are reciprocally interconnected. These two areas appear to lie at the anatomical border between visual perception and visual memory. Studies of monkeys indicate that perirhinal cortex is important for the memory aspect of recognition memory. Area TE appears to be important for the visual processing that enables the perceptual ability required for successful visual recognition memory (Buffalo et al. 1999, 2000). The functional dissociations that have been reported between the effects of damage to area TE and the effects of damage to perirhinal cortex support these conclusions. For example, monkeys with damage limited to the perirhinal cortex exhibited delay-dependent memory impairment on both visual and tactile versions of the DNMS task (normal performance at short delays when the

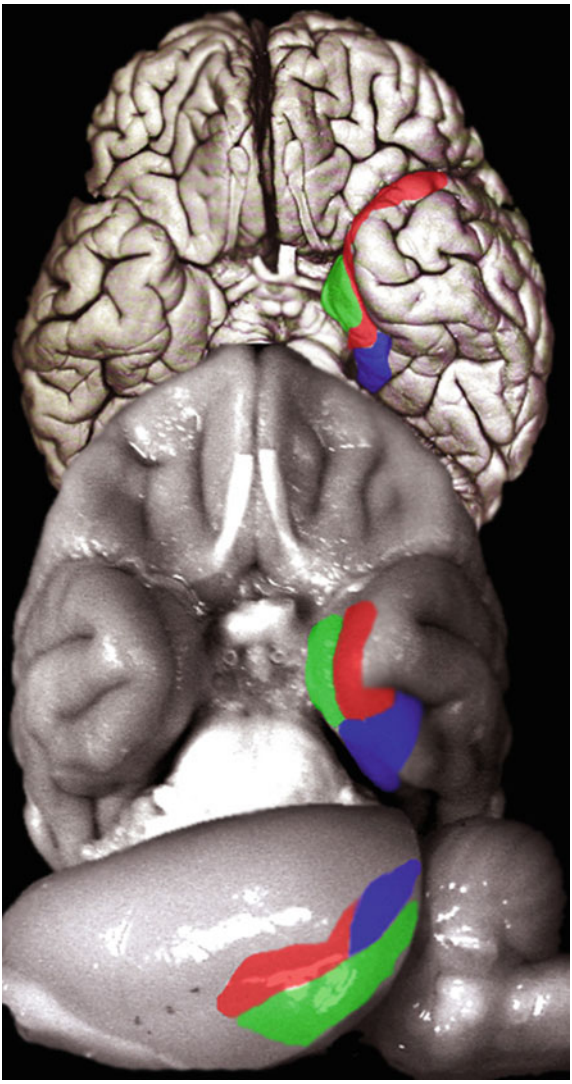

Fig. 2 A ventral view of a human brain (top), a ventral view of a monkey brain (middle), and a lateral view of a rat brain (bottom). The colored structures represent the major cortical components of the medial temporal lobe in all three species: entorhinal cortex (green), perirhinal cortex (red), and parahippocampal cortex (in primates; blue) or postrhinal cortex (in rats; blue). The organization of these structures is highly conserved across these three species

demand on memory is minimal, but impaired performance at longer delays when the demand of memory is greater)—indicating that the primary impairment is mnemonic. By contrast, monkeys with damage restricted to area TE were impaired on visual DNMS but not tactile DNMS (Buffalo et al. 1999). That is, the

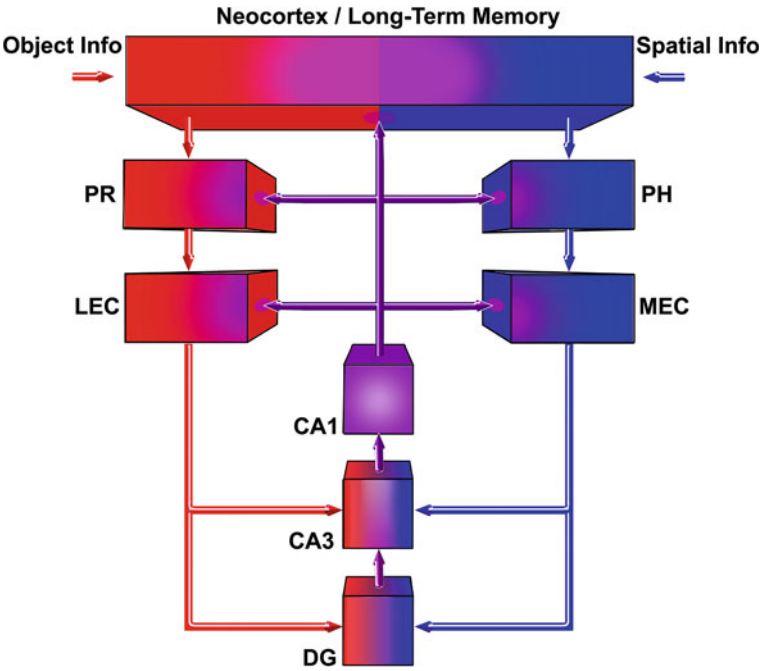

Fig. 3 A schematic view of the medial temporal lobe memory system: The system is hierarchically organized. The hippocampus, defined here as the dentate gyrus (DG), CA3, and CA1, is anatomically situated to receive highly processed information from widespread neocortical regions through four medial temporal cortical areas: the lateral entorhinal cortex (LEC), medial entorhinal cortex (MEC), perirhinal cortex (PR), and parahippocampal cortex (PH; in the rat the postrhinal cortex is used in place of the parahippocampal cortex). Long-term memory (LTM) is thought to be stored in the neocortical areas that were initially involved in processing the various types of sensory information that allowed the encoded experience. Neocortical sensory information is further processed by medial temporal lobe neocortical structures before being relayed to the hippocampus. The DG and CA3 of the hippocampus are anatomically positioned to integrate this information. CA1, primarily through projections to the subiculum (not illustrated), sends this information out of the hippocampus to ultimately contribute the neocortical storage of LTM. In this example, objection information (shown in red) reaches the hippocampus via the PR and LEC. Spatial information (shown in blue) reaches the hippocampus via the PH and MEC. This information is combined in the hippocampus and sent back to neocortex (shown in purple) where it is integrated into LTM. Retrieval of the neocortical LTM is initially dependent on the hippocampus, but through a process of systems consolidation, eventually becomes hippocampus-independent

impairment after TE lesions was unimodal, not multimodal and suggestive of an impairment that is selective to visual perception.

Further, monkeys with perirhinal cortical lesions acquired an automated version of visual DNMS as quickly as normal animals when the delay between sample and choice was only 0.5 s (Buffalo et al. 2000). This finding showed that the ability to perceive the stimuli was unaffected by perirhinal lesions and that monkeys could perform normally when the memory demand was minimal (i.e., the delay was short). In contrast, monkeys with TE lesions were robustly impaired at the 0.5 s delay. Accordingly, monkeys with TE lesions failed even when the memory

demands of the task were minimal. The parsimonious explanation of this result is that the monkeys with area TE lesions had difficulty processing the visual stimuli. These findings and others like them (e.g., Buffalo et al. 1999) indicate that perirhinal cortex, like other medial temporal lobe structures, is important for the formation of memory, while area TE is important for visual perceptual processing. Today, it is undisputed that the perirhinal cortex plays a critical role in recognition memory (Buffalo et al. 1999, 2000; Meunier et al. 1993; Eacott et al. 1994; Prusky et al. 2004; Mumby and Pinel 1994; Kornecook et al. 1999; Nemanic et al. 2004; Bussey et al. 1999, 2000; Ennaceur et al. 1996; Winters and Bussey 2005).

Like the perirhinal cortex, the hippocampus has been implicated as important for recognition memory. In fact, the title of the classic paper by Scoville and Milner (1957) was "Loss of recent memory after bilateral hippocampal lesions." The title certainly implies that the memory loss inpatient H.M. was due to the direct damage to the hippocampus. Note however that the last paragraph of the manuscript clearly states correctly, "It is concluded that the anterior hippocampus and hippocampal gyrus, either separately or together, are critically concerned in the retention of current experience." It is interesting that despite the indication that the memory impairment should not be attributed to the hippocampus itself, most subsequent work focused on the hippocampus to the exclusion of the neocortical areas of the medial temporal lobe.

In the 1990s, investigators began using stereotaxic neurosurgical methods to selectively damage the hippocampus in monkeys and to test for recognition memory impairments (Alvarez et al. 1995; Murray and Mishkin 1998; Beason-Held et al. 1999; Zola et al. 2000; Nemanic et al. 2004). The studies concluded that selective hippocampal lesions impair recognition memory (but see Murray and Mishkin 1998). Importantly, Zola et al. (2000) gathered data from 18 monkeys with bilateral lesions of the hippocampus made either by an ischemic procedure, by radio frequency, or by ibotenic acid. Significant recognition memory impairment was observed at all the delays that were tested from 15 s to 40 min. Other work in monkeys using memory tests of spontaneous preference supports the conclusion that selective hippocampal lesions produce robust delay-dependent memory impairment (Zola et al. 2000; Nemanic et al. 2004). These data are congruent with work in humans with damage that included the hippocampus using similar spontaneous recognition memory tests (McKee and Squire 1993; Pascalis et al. 2004). However, work in rodents with selective hippocampal lesions when tested on the DNMS task, has been more mixed. Several studies in the rat have reported that bilateral damage to the hippocampus or the fornix impairs recognition memory (Mumby et al. 1992; Mumby et al. 1995; Wiig and Bilkey 1995; Clark et al. 2001; Prusky et al. 2004). Other studies have failed to find an impairment following bilateral hippocampal or fornix lesions (Aggleton et al. 1986; Rothblat and Kromer 1991; Kesner et al. 1993; Mumby et al. 1996; Duva et al. 1997). A consideration of all the studies suggests that impaired performance on the DNMS task typically occurs following hippocampal damage if the delay is sufficiently long and if the hippocampal lesions are sufficiently large—although these factors alone do not reconcile all the available data (see Clark et al. 2001). I note however that the

observed impairment is often relatively mild, although nonetheless significant (Broadbent et al. 2009).

There is a substantial literature reporting that recognition memory impairments following hippocampal damage or disruption in rats and mice when tested using spontaneous preference tasks (Baker and Kim 2002; Broadbent et al. 2004; Clark et al. 2000; de Lima et al. 2006; Gaskin et al. 2003; Hammond et al. 2004; Ainge et al. 2006; Rampon et al. 2000; Rossato et al. 2007). These findings all support the idea that the hippocampus is important for familiarity-based recognition memory. Yet there is also a literature, using spontaneous preference tasks in the rodent suggesting that the hippocampus is not needed for recognition memory (Winters et al. 2004; Forwood et al. 2005; Mumby et al. 2005; O'Brien et al. 2006). It will be important to identify the critical factors that determine when the hippocampus is important for recognition memory and when (or if) normal recognition memory can be accomplished in the absence of the hippocampus (for further discussion of this issue and literature see, Winters et al. 2008). Accordingly, a consensus has not been achieved in the rodent with respect to the role of the hippocampus in recognition memory.

3 Current Topics

3.1 Does Perirhinal Cortex Exclusively Support Memory, or Memory and Higher Order Visual Perception?

As noted above, structures within the medial temporal lobe are critically important for memory. Across several decades, behavioral studies of memory-impaired patients, monkeys, and rodents with bilateral damage to these structures have documented a striking impairment in memory, which occurs against a background of ostensibly preserved perceptual functions (Milner et al. 1968; Squire and Wixted 2011; Mishkin 1982). However, this view has been challenged by a literature suggesting that the perirhinal cortex (a medial temporal lobe neocortical structure) is important not only for memory, but may also have a fundamental role in certain types of high-level visual perception (e.g., Bussey and Saksida 2005; Lee et al. 2005). Specifically, it has been argued that the perirhinal cortex is necessary to resolve visual object discriminations when these discriminations contain a high degree of feature overlap, referred to as feature ambiguity (Bussey et al. 2002; Barense et al. 2005).

This idea emerged from work in the monkey (Eacott et al. 1994). Monkeys with bilateral lesions of the entorhinal and perirhinal cortex were impaired on both a 0 s delay and in a simultaneous matching condition. The authors suggested that these findings might reflect the requirement of the perirhinal cortex to identify stimuli when the stimuli are perceptually similar, because the stimuli used in this study shared many overlapping features. Subsequent work in the monkey was designed

specifically to examine the possible contribution of the perirhinal cortex to visual perception. In these studies, various attributes of the stimuli were systematically manipulated during visual discrimination learning tasks to assess the performance of monkeys with lesions of the perirhinal cortex. Impairments were only observed when the visual discriminations involved stimuli with high feature overlap and where good performance appeared to require relatively complex object-level perception (Buckley and Gaffan 1998, 2006; Buckley et al. 2001; Bussey et al. 2002, 2006).

Studies in humans with medial temporal lobe lesions have also addressed this issue, sometimes finding impaired performance and sometimes finding intact performance on these high-level discrimination tasks (Lee et al. 2005; Shrager et al. 2006, respectively). Notably, a comprehensive review (Suzuki 2009) suggested that a reason the issue has been difficult to resolve inpatient studies is that the locus and extent of damage varies among studies, and patients with perceptual impairments might have damage to lateral temporal cortex in addition to medial temporal lobe damage and this extra damage would be expected to impair visual perception. Using the experimental animal, where behavior can be tested after targeted and circumscribed lesions limited to perirhinal cortex, could circumvent these difficulties. However, studies in animals are also problematic. In order to study perceptual ability in animals, the perceptual manipulations must be imbedded within a memory task. In other words, in order to evaluate perceptual function in these studies, animals must typically be trained on a memory task that requires the acquisition of new information in order for the perceptual task to be performed. Accordingly, it is difficult to disambiguate impaired learning and memory from impaired perception using animal studies and difficult to resolve the issue in human studies because of differences in brain lesions and the difficulty in quantifying those lesions even by using modern imaging methods (see Suzuki 2009).

Perhaps the best approach would be to use experimental animals (where the brain lesions can be controlled), but with an experimental design where the influence of any potential mnemonic effect is minimized while still evaluating complex visual perceptual abilities. Accordingly, a novel behavioral paradigm for the rat made it possible to separate the evaluation of memory functions from the evaluation of perceptual functions (Clark et al. 2011). Here, rats were given extensive training on an automated two-choice discrimination task. The extensive training maintained memory performance at a high level during which interpolated probe trials tested visual perceptual ability.

The probe trials were designed to systematically vary the degree of feature ambiguity (i.e., feature overlap) between the two stimuli by morphing the two stimuli into one another across 14 levels of difficulty. As feature ambiguity was increased from very little ambiguity to extreme ambiguity, performance declined in an orderly and monotonic curve that ranged from 87% correct to 50% at the most difficult level. If the perirhinal cortex were critical for feature ambiguous discriminations, then performance should have been intact at the lower morph ambiguity levels and progressively impaired as the stimuli began to share more features and become more difficult/ambiguous. This was not the finding. Bilateral lesions of the

perirhinal cortex completely spared the capacity to make these difficult discriminations at every difficulty level (Clark et al. 2011). Control procedures ruled out the possibility the rats were using local cues to solve the discriminations (which would have prevented feature ambiguous, high-level object discriminations from being evaluated). When these same animals were then tested on a recognition memory task, the perirhinal lesions impaired memory—thus confirming the memory impairment caused by these lesions.

Accordingly, the tactic to reduce the possible influence of learning and memory impairment on perceptual performance proved to be successful. Instead of training many discriminations and then presenting a single probe trial for each discrimination, as has been done in the past (Hampton and Murray 2002), animals were trained to learn a single discrimination and then, while maintaining a high level of performance, present 150 probe trials at each of 14 different levels of feature ambiguity. These data suggest that rats with perirhinal cortex lesions exhibited intact performance on every probe trial level because performance did not require any new learning. The basic discrimination was very well learned, and performance remained high throughout testing. These findings provide strong support that the perirhinal cortex is not important for any form of visual perceptual abilities and highlight the value in minimizing the influence of memory impairment when testing perception in the experimental animal. They also explain why prior work in the experimental animal initially reported perceptual impairments. These impairments were likely memory impairments masquerading as perceptual impairments (see Hales et al. 2015 for detailed discussion of these issues). Nonetheless, the topic is still debated and now includes an evaluation of the electrophysiological characteristics of the perirhinal cortex and how both memory and perceptual firing patterns can be inferred (Ahn and Lee 2017).

3.2 *Is There an Anatomical Separation Between Recollection and Familiarity?*

Recognition memory is commonly viewed as consisting of two components, familiarity and recollection (Mandler 1980). Familiarity involves only knowing that an item was presented without possessing any additional information about the learning episode. Recollection, on the other hand, involves remembering specific contextual details about a prior learning event.

When Brown and Aggleton (2001) proposed a neuroanatomical basis for these two processes, interest in this distinction increased dramatically. Specifically, they proposed that recollection depends on the hippocampus whereas familiarity depends on the adjacent perirhinal cortex. Later work has elaborated on this same proposal (Rugg and Yonelinas 2003; Aggleton and Brown 2006; Eichenbaum et al. 2007), and it has become the basis for the design and analysis of a substantial amount of subsequent experimental work. Importantly, however, alternative

formulations have also been suggested regarding the basis of recognition memory and its anatomy (Wixted 2007; Squire et al. 2004).

Much of the discord can be related to the fact that much work taken to support Brown and Aggleton's proposal (2001) have been interpreted in terms of models of recognition memory that are controversial. The implications of these very studies change when the findings are evaluated in terms of an alternative, yet commonly supported model based on signal detection theory.

There have been a large number of studies that have used a variety of neuroscientific methods such as brain lesions, electrophysiological recordings of single neurons, and fMRI, across work with humans, monkeys, and rodents that have evaluated the functional organization of the medial temporal lobe. Much of this work has been originally interpreted in terms of a distinction between recollection and familiarity. However, these same results can also be more simply interpreted with respect to memory strength and indicate that the structures of the medial temporal lobe function in a more integrated and cooperative manner than proposals about the distinction between the hippocampus and perirhinal cortex and recollection and familiarity would suggest.

Receiver Operating Characteristic (ROC) analysis is associated with signal detection theory and was first applied to the analysis of recognition memory more than half century ago (Egan 1958). However, more recently, this analysis has been applied to the neuroanatomical foundations of recollection and familiarity. Briefly, signal detection theory posits that targets (correct items on a recognition memory test) and foils (incorrect or lure items on a recognition memory test) have overlapping distributions of memory strength and the strength and variance of the targets tend to be greater than that of the foils. This model is based on the assumption that familiarity and recollection are both continuous processes that determine the memory strength of a test item (e.g., Mandler 1980; Rotello et al. 2004; Wixted 2007).

A newer two-component theory that also addresses ROC data posits that recollection is a high-threshold component process. In other words, recollection is assumed to support a high-confidence belief that an item has been encountered before (Yonelinas 1994). Additionally, familiarity is thought to be a signal detection process that supports a backup role whenever recollection is absent. Importantly, this high-threshold, signal detection model posits that individual recognition decisions are based on either recollection or on familiarity, but not on a combination of the two.

Using this model (Yonelinas 1994) to evaluate and interpret ROC data, several studies have suggested that hippocampal lesions selectively impair recollection (Aggleton et al. 2005; Daselaar et al. 2006; Fortin et al. 2004; Yonelinas et al. 1998, 2002). The critical point is the asymmetry of the ROC curve is more pronounced in healthy subjects than for amnesic patients with hippocampal damage. The extent to which asymmetry is observed is thought to be the benchmark of recollection in the high-threshold signal detection model (Yonelinas 1994), whereas the more symmetrical ROC produced by amnesic patients is supposed to indicate that their recognition performance is based more on familiarity than is the performance of

healthy controls. In fact, familiarity-based performance is often estimated to be normal in the amnesic patients in these studies.

However, in a traditional signal detection theoretical account, a symmetrical ROC only reflects a weak memory, not the absence of recollection. Additionally, an asymmetrical ROC simply implies that the target and foil distribution have an unequal variance, which is tantamount to a strong memory and thus need not suggest that recognition is only supported by recollection (Heathcote 2003; Slotnick and Dodson 2005; Rotello et al. 2005; Smith and Duncan 2004). The analyses of Remember/Know (R/K) judgments have also been used to evaluate the neuroanatomical basis of recollection and familiarity. In the R/K paradigm, subjects must make a judgment as to whether an item is old or new. Then for each old item, they are asked if they "remember" the item (a proxy for recollection) or if they simply "know" that the item had been previously presented (a proxy for familiarity). A number of studies using the R/K method have indicated that hippocampal lesions robustly impair recollection/remember, but impair familiarity/know judgments to a much lesser degree, or in some cases, not at all (Aggleton et al. 2005; Holdstock et al. 2002, 2005; Moscovitch and McAndrews 2002; Yonelinas et al. 2002). However, an obvious concern is that these interpretations would only be valid if the subjective judgments of "Remember" and "Know" are reliable and accurate proxies for recollection and familiarity, respectively.

Importantly, signal detection theory addresses R/K judgments differently (Donaldson 1996; Dunn 2004; Wixted and Stretch 2004). Here, a reduction in "remember" responses combined with little or no reduction in "know" responses is a natural result of strong memories becoming weak memories (see Fig. 2, Squire et al. 2007). In other words, a disproportionate reduction in "remember" judgments need not require a specific loss of recollection. In fact, there is now substantial support for the idea that R/K judgments are an index of memory strength and are not reliable proxies for the qualitatively different processes of recollection and familiarity (Donaldson 1996; Dunn 2004; Rotello et al. 2006; Wixted and Stretch 2004; Wais et al. 2006, 2010).

Accordingly, this collection of findings suggests that the methods that have generally been used to distinguish between recollection and familiarity, might rather distinguish strong memories from weak memories. Further, the functions of the hippocampus and the functions of the perirhinal cortex cannot be crisply dichotomized into the realms of recollection and familiarity, respectively. However, this statement should not be taken to suggest that these two structures function in the same way. For example, neurons in the hippocampus tend to be responsive to more familiar stimuli (Viskontas et al. 2006), whereas neurons in the perirhinal cortex tend to respond to novelty and this response declines as the stimuli become more familiar (Xiang and Brown 1998). At present, it is not clear what data like these indicate about the functional organization of the hippocampus and perirhinal cortex, but they would not appear to relate to anatomical distinctions between recollection and familiarity. A review of the electrophysiological and fMRI literatures instead suggests that both recollection and familiarity signals are apparent in both the hippocampus and perirhinal cortex and that a better approach to understanding

these signals would be to evaluate how specific attributes of the stimulus items are encoded into various aspects of the overall memory representation and how these representations may functionally differ between different components of the medial temporal lobe, including the hippocampus and perirhinal cortex (Eichenbaum et al. 1999; Naya et al. 2003; Wood et al. 1999; Lech and Suchan 2013).

3.3 *Is the Organization of Spatial Memory Different Between Humans and Rats, or Is the Difference Between the Working Memory Capacities of the Two Species?*

As described above, declarative memory depends critically on the hippocampus and anatomically associated structures in the MTL. However, these structures, and in particular, the hippocampus, have been strongly associated with the formation and storage of spatial memory (O'Keefe and Nadel 1978; Moser et al. 2008). A current topic of debate relates to the idea that these two perspectives are not fully compatible (Eichenbaum and Cohen 2014; Buffalo 2015). The discord centers on the fundamental distinction between working memory and long-term memory. Working memory is the ability to hold a limited amount of information "in mind" for a limited amount of time after encoding (Baddeley 2003; Cowan 2001; Warrington and Taylor 1973). This information content can be extended in time by active maintenance. The classic example is remembering a new phone number long enough to dial the phone. The average number of digits humans can hold in working memory is 7 (the original length of a phone number), but this number changes depending on the type of information being held. For example, humans can only hold 4 objects, or 1 face in working memory at any given time (Baddeley 2003; Cowan 2001; Warrington and Taylor 1973). Working memory has been thought to be independent of the hippocampus and other MTL structures because it is intact following MTL damage (Milner 1972; Baddeley and Warrington 1970; Clark et al. 2000, 2001; Jeneson and Squire 2012). Thus, tasks that could be maintained by working memory, including spatial tasks, should be intact following MTL damage. However, if MTL structures are necessary to produce the computations required by spatial tasks, then MTL damage should always impair performance on spatial tasks irrespective of the availability of working memory. If true, then for spatial tasks, the distinction between working memory and long-term memory would be irrelevant. Work in humans has been very clear on the issue. For example, work with patients with MTL damage has indicated normal performance on spatial memory tasks under conditions where working memory appears to have supported the performance (Shrager et al. 2008; Jeneson et al. 2010; Kim et al. 2013). Indeed, the noted patient E.P. demonstrated strikingly good performance on spatial navigation when asked about his childhood neighborhoods (Teng and Squire 1999). One type of spatial task is path integration (also known as dead reckoning;

Darwin 1873). In the rodent version of path integration, rats search for food in the dark and then innately attempt to return to the refuge of their start location in order to consume the food. The accuracy with which they return to their start location is the measure of the success of their path integration. Notably, studies of path integration in rats with hippocampal (or entorhinal) damage have reported clear impairments (Maaswinkel et al. 1999; Whishaw et al. 2001; Save et al. 2001; Parron and Save 2004). Importantly, however, all of these studies failed to report the length of time it took for the rats to complete the trials. This means that the rats in these studies may have performed normally whenever the trials were completed quickly because in those instances, performance might have been sustained by their intact working memory.

To address this issue, a new analytical method was developed so that short trials, where performance might be sustained by working, could be analyzed separately from longer trials that would require long-term memory (Kim et al. 2013). Further, the test was administered to both rats with hippocampal damage and humans with hippocampal damage (Kim et al. 2013). The findings from the human section of the study reported that when the trials were simple (that is the target was found quickly), patients with hippocampal damage performed as well as healthy controls. However, rats performed at chance levels even on the simplest trials where the food was found within 3 s or the distance to find the food was 1 m or less, and involved zero turns. These data indicate that rats are unable to use working memory to support performance on this hippocampus-dependent spatial task the way humans do (Kim et al. 2013), and the way rats do on nonspatial, hippocampus-dependent tasks (Clark et al. 2000, 2001).

The implication of this finding and others like them is that spatial memory is organized differently in the rat and human brain. In fact, work with humans clearly suggests that there is nothing unique about spatial memory. Spatial memory is just another form of declarative memory. And like other forms of declarative memory, it is impaired by hippocampal damage, but normal when working memory can be used to support it. Currently, it is not uncommon for scientists who study hippocampal function in the rodent to view the hippocampus exclusively as a spatial processing structure. However, if spatial memory were organized in a fundamentally different way between humans and rats, this would present a very serious challenge for research using rodents as a model system for human hippocampal function (Clark and Squire 2010, 2013).

However, there are at least two other possible explanations for the discrepant finings between humans and rats with respect to spatial memory that do not involve surmising that spatial memory is organized differently between the two species. First, spatial working memory like that required for path integration may be unavailable or perhaps impoverished because the neocortex of the rodent lacks the capacity to construct and maintain a coherent working memory of a spatial environment. Note that in order for subject to use spatial information, a large number of individual components of an environment need to be represented and organized into a meaningful whole. The amount of information necessary for representing a spatial environment may be within the capacity of the grossly expanded neocortical

working memory areas of the human brain, but outside of the limits of the rodent neocortical working memory areas. These issues would not apply to nonspatial tasks, because the information that must be maintained in working memory is simpler than in spatial tasks (Clark et al. 2000, 2001).

If working memory capacity was insufficient, then normal rats might accomplish spatial memory tasks, like path integration, by relying exclusively on long-term memory. Rats with hippocampal lesions are impaired at forming long-term memory so they would be impaired on any task, spatial or otherwise, where the information necessary for the task exceeds the capacity of working memory. Similarly, as has been suggested by others, some forms of spatial working memory might depend on the interaction between the medial prefrontal cortex (mPFC) and the hippocampus (Gordon 2011; Hyman et al. 2010; Jones and Wilson 2005; Spellman et al. 2015). Here, hippocampal lesions would disrupt this interaction and impair spatial working memory.

To address these considerations, Sapiurka et al. (2016) tested rats with either mPFC lesions or hippocampal lesions on three tasks of spatial or nonspatial memory: spatial alternation, path integration, and a novel, nonspatial task that required alternation between two different odor-scented cups. The rationale was that if rats do not have sufficient working memory to support spatial tasks, then spatial tasks must always be accomplished by long-term memory. Thus, brain lesions that impair working memory, like lesions of the mPFC, should not affect a spatial task like path integration. Rats were also tested on spatial alternation, a classic working memory task. The results showed that rats with hippocampal lesions were impaired on path integration whereas rats with mPFC were normal (Sapiurka et al. 2016). This finding suggests that path integration in rats is accomplished exclusively by long-term memory and not by working memory. In this study, both groups were impaired on spatial alternation. Here, the interpretation is more complicated. The rats with mPFC lesions were impaired because spatial alternation is a working memory task and mPFC is important for working memory (Horst and Laubach 2009; Hyman et al. 2010; Gordon 2011; Spellman et al. 2015). The rats with hippocampal damage were impaired on spatial alternation because the spatial information exceeded their working memory capacity. Rats with mPFC lesions could not use long-term memory to solve the alternation task because the high interference of repetitive tasks like alternation require working memory (Kane and Engle 2002; Granon et al. 1994). That is, during path integration each trial is unique, whereas each trial of the alternation tasks is dependent on information obtained from the previous trial, and the same response was repeated multiple times in each session (which would cause high interference). Finally, on the nonspatial working memory task (odor alternation), rats with mPFC lesion were again impaired on this working memory task because mPFC supports working memory. However, animals with hippocampal lesions were unimpaired because the odor information was simple enough to be maintained rodent working memory.

In summary, it remains possible that human and rodent spatial memory is fundamentally organized in a biologically different way between the two species. However, the data outlined above suggest that a reasonable, and perhaps

parsimonious, alternative perspective is that because of the complex nature of spatial information, limited rodent working memory is unable to support memory tasks that require spatial information and that these tasks necessarily require the use of long-term memory. Rats with hippocampal lesions fail at spatial tasks not because a spatial processing organ has been damaged, but because they are unable to rely on long-term memory. In this regard, the discord between the rodent and human studies is due simply to a difference in the capacity of working memory between the two species (Sapiurka et al. 2016).

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