



A new view of the medial temporal lobes and the structure of memory

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Abstract

Recent research in cognitive neuroscience has supported the idea that active rehearsal of information over short delays, or working memory maintenance, is accomplished by activating long-term memory representations. Nonetheless, it is widely assumed that although the human hippocampus and related medial temporal lobe structures may be critical for the formation of long-term memories, they are not involved in working memory maintenance. Here, we reconsider this issue and review evidence suggesting that humans and nonhuman primates with large medial temporal lobe lesions have difficulty retaining complex, novel information even across short delays. These results suggest that perirhinal and entorhinal regions, and under some circumstances, even the hippocampus, may be necessary for some forms of working memory as well as long-term memory. Moreover, neurophysiological and neuroimaging evidence suggests that all of these medial temporal regions exhibit activity associated with the active maintenance of novel information. Finally, we review a neurally plausible computational model of cortico-hippocampal interactions that points to a special role of the hippocampus in the representation of relational codes in memory. Our analyses suggest that the hippocampus plays this special role not only in episodic long-term memory, but also in working memory maintenance. Collectively, these results are consistent with the hypothesis that the active maintenance of complex, novel information is accomplished through the sustained activation of long-term memory representations bound together by the hippocampus and medial temporal cortical regions.

Keywords: Hippocampus, medial, temporal, prefrontal, working, short-term, long-term, episodic, memory, fmri, neuroimaging, neurophysiology, lesion, human, primate, computational modeling, cortico-hippocampal interactions.

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Introduction

In 1957, Scoville and Milner published a case report of a patient they named “H.M.”, who had undergone a bilateral medial temporal lobe (MTL) resection for the treatment of intractable epilepsy (Scoville and Milner, 1957). This case report revolutionized the study of memory for two reasons: First, following the surgery, H.M. was left with a dense anterograde amnesia, and was thus virtually unable to form new memories for events, or episodic memories (Scoville and Milner, 1957). This finding identified the MTL as a region critical for new memory formation. Second, clinical testing indicated that H.M., along with other patients who underwent temporal lobectomies, could retain small amounts of information over a few seconds, in the absence of distraction (Penfield and Milner, 1957; Scoville and Milner, 1957; Drachman and Arbit, 1966). This finding was critical to the development of views regarding the structure of memory.

At that time, a great deal of behavioral research in experimental psychology was accumulating to suggest that memory might not be characterized by a single, undifferentiated store (Drachman and Arbit, 1966). The findings from patient H.M. were more consistent another hypothesis-- that immediate memory for information across short delays might neurally and functionally independent from the retention of information over longer intervals (Atkinson and Shiffrin, 1971). Building on this work, Baddeley and Hitch (Baddeley and Hitch, 1974) introduced an influential model of "working memory." According to this model, rehearsal of different forms of information is mediated by different short-term buffers (i.e., visuospatial and phonological), and each of these buffers was distinct from long-term memory. This multi-store model of memory is analogous to a computer, in which processing and storage are segregated-- information is more or less permanently stored on a hard disk, with a random access memory (RAM) buffer used for the manipulation of active elements.

In the time since the introduction of the multi-store view of memory, several researchers have proposed that working memory maintenance may actually be accomplished by activating stored (i.e., long-term) memory representations, rather than by transferring information to distinct short-term buffers, (Goldman-Rakic and Friedman, 1991; Shastri and Ajjanagadde, 1993; Petrides, 1994; Fuster, 1995; 1997; Cowan, 1997; Eichenbaum and Cohen, 2001). For example, numerous studies suggest that visual imagery and object and spatial working memory are supported by the same neural systems that support visual object and spatial perceptual processing (Fuster and Jervey, 1981, 1982; Fuster et al., 1985; Quintana et al., 1989; Chafee and Goldman-Rakic, 1998; Postle and D'Esposito, 1999; O'Craven and Kanwisher, 2000). Indeed, these views parallel the development of neurally motivated connectionist models of cognition in which information processing and storage are inextricably linked (Feldman and Ballard, 1982; McClelland and Rumelhart, 1985; Shastri, 1988; Shastri and Ajjanagadde, 1993; Rolls, 2000; Renart et al., 2001).

Despite these developments, distinctions between working and long-term memory have been defended, in large part, by the idea that the primate MTL region is important for episodic memory formation, but not for working memory maintenance (Sidman et al., 1968; Wickelgren, 1968; Cave and Squire, 1992). This view is bolstered by numerous imaging studies that don't show hippocampal activity during WM tasks, and many patient studies that show MTL patients with intact WM function. Here, we reconsider this issue based on a review of lesion, neurophysiological, and neuroimaging studies of human and nonhuman primates. These findings

suggest that under some circumstances, regions in the primate MTL may play an essential role for both working and long-term memory.

Lesion studies

As noted earlier, clinical testing of H.M. and other amnesic patients suggested that these patients had intact short-term memory, but impaired long-term memory (Drachman and Arbit, 1966; Sidman et al., 1968; Wickelgren, 1968; Baddeley and Warrington, 1970; Cave and Squire, 1992). Stimuli in these studies included verbal information, simple nonverbal figures, or spatial information. However, in even early studies of the amnesic syndrome, some evidence emerged to suggest that working memory deficits were apparent when more complex stimuli and tasks were used (Drachman and Arbit, 1966). For example, detailed memory for shapes (Sidman et al., 1968) and faces (Warrington and Taylor, 1973) was impaired at short as well as long delays. Some researchers suggested that these discrepancies might be due to frontal lobe dysfunction in patients with amnesia due to Korsakoff's syndrome or severe intractable epilepsy (Baddeley and Warrington, 1970; Cave and Squire, 1992).

Studies of nonhuman primates with MTL lesions, however, suggested that not all forms of short-term memory are intact following large medial temporal lesions. For example, the delayed matching or nonmatching to sample (DMS and DNMS, respectively) requires the retention of a sample object across a delay (Konorski, 1959; Gaffan, 1974; Mishkin and Delacour, 1975). After the delay, the subject is shown the sample object, along with a novel object, and is rewarded either for choosing the sample (DMS) or the novel (DNMS) object. This task was initially developed to explore short-term memory over spans of seconds (Konorski, 1959), but was adapted to be more like tests of long-term recognition memory in humans. The adaptation was to use a large set of complex stimuli, so that on every trial, the stimulus to be remembered and the foil object were to be trial-unique (Gaffan, 1974; Mishkin and Delacour, 1975). Accordingly, the task could be solved by actively maintaining the sample across the delay, remembering the sample object during the memory decision, or by merely recognizing the difference in familiarity between the sample and foil objects during the memory decision.

Using these types of tasks, several researchers noted that large MTL lesions caused delay-dependent memory deficits. Specifically, researchers noted that performance of monkeys with large MTL lesions appeared to be intact at short delays (less than 8s) and impaired at long delays (15s or more), suggesting that the procedure selectively affected LTM (Mishkin, 1978; Mahut et al., 1982; Murray and Mishkin, 1984; Zola-Morgan and Squire, 1985; Murray and Mishkin, 1986; Zola-Morgan and Squire, 1986; Zola-Morgan et al., 1993; Meunier et al., 1996). However, this conclusion was limited by several factors. For example, impairments in several studies were observed at relatively short delays (10-15s) that could possibly be bridged by working memory maintenance in monkeys (Fuster and Alexander, 1971) and certainly in humans (Chao and Knight, 1995). Furthermore, memory deficits at short delays may have been underestimated because of two factors. First, near-ceiling performance compressed the variability of intact controls at the shortest delays, thus limiting the degree to which control and lesion groups could differ (Ringo, 1988, 1991). Second, in many studies, monkeys were trained to a performance criterion on short-delay trials before proceeding to experimental testing (Ringo, 1993; Horel, 1994). In an analysis of results across two different laboratories, Ringo (1993) observed strong (.82-.85) correlations between the number of trials-to-criterion at the short delay

and the difference between lesioned and control monkeys at long delays. These findings strongly suggest that, even when memory deficits were selectively observed at long delays, MTL regions might have also made a contribution at short delays, as reflected in the differential number of trials-to-criterion.

In evaluating these findings, it is also important to note that the MTL regions implicated in memory formation include not only the hippocampus, but also the entorhinal, perirhinal, and parahippocampal cortices that provide the hippocampus with most of its cortical input (Suzuki, 1996; Lavanex and Amaral, 2000). Specifically, the parahippocampal and perirhinal cortices provide the majority of cortical input to the entorhinal cortex, which in turn, provides the predominant source of cortical input to the dentate gyrus and hippocampal subfields. Although it is likely that the formation of complex episodic memories requires the joint participation of all of these regions (Zola-Morgan et al., 1994; Rempel-Clower et al., 1996), the differential neuroanatomy and neurophysiology of these regions also suggests that each may make a distinct contribution (Aggleton and Brown, 1999; Eichenbaum and Cohen, 2001).

In light of the anatomical heterogeneity of the MTL, it is not surprising that studies using more focal lesions reported that damage to different MTL regions had different effects on memory. Specifically, results showed that damage to the perirhinal, parahippocampal, and entorhinal cortices caused severe trial-unique DNMS impairments (Murray and Mishkin, 1986; Zola-Morgan et al., 1989b; Suzuki et al., 1993; Zola-Morgan et al., 1993; Meunier et al., 1996), with deficits in one study apparent even with no delay (Eacott et al., 1994). Focal hippocampal lesions produced by radiofrequency or excitotoxic methods also caused DNMS impairment, but these effects were much more mild than those seen after perirhinal lesions. (Murray and Mishkin, 1998; Zola et al., 2000). Nonetheless, meta-analyses of these studies suggest that even focal hippocampal lesions may cause a mild DNMS deficit across all delays (Zola et al., 2000; Baxter and Murray, 2001a) (although the relationship between extent of hippocampal damage and performance remains controversial—see (Zola et al., 2000; Baxter and Murray, 2001a, b; Zola and Squire, 2001)). In a similar vein, disruption of the hippocampus through fornix transection also caused a mild DNMS impairment (Gaffan, 1974; Owen and Butler, 1981; Mahut et al., 1982; Zola-Morgan et al., 1989a), sometimes only apparent at very long delays (minutes).

In summary, although disagreement remains regarding the functional memory deficit produced by lesions of the hippocampus versus surrounding cortical regions, a few consistencies emerge in the literature: First, the DNMS deficit produced by hippocampal lesions is not as severe as the deficit produced by lesions to the surrounding perirhinal, entorhinal, and parahippocampal cortices. Second, combined damage to all of these regions affects memory even across short delays that could be bridged in intact animals by working memory maintenance. Putting these findings together, the results suggest that the hippocampal formation and surrounding structures may make different contributions to memory processing, but these regions may collectively support memory across short and long delays. Accordingly, these findings call into question the initial view that short-term memory is intact in MTL amnesia. How can these views be reconciled?

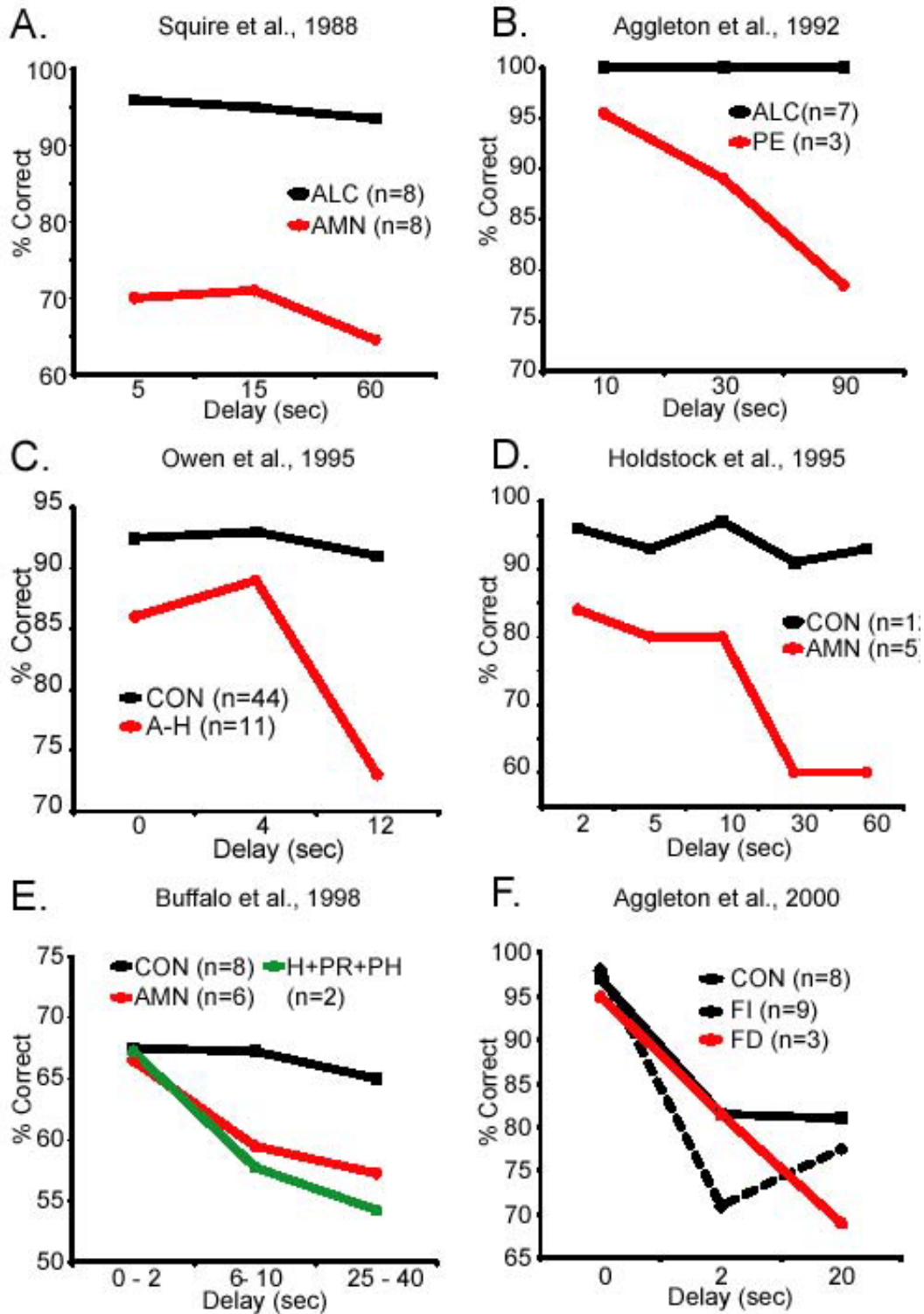


Figure 1. Summary of all studies examining retention of novel information across short delays in patients with MTL damage.

As noted earlier, most studies of short-term memory in human amnesics used simple, familiar stimuli. In contrast, a critical feature of the DNMS task used was that the stimuli were complex, novel, trial-unique objects. Thus, it is possible that the usage of complex, novel stimuli placed particular demands on processing implemented by the MTL region. For example, whereas short-term memory for familiar verbal stimuli could be mediated by maintaining well-learned visual, semantic, and phonological codes that are stored outside of the medial temporal region, short-term memory for complex, novel stimuli may require the active maintenance of codes that are uniquely stored in the medial temporal region. If the latter is true, one would expect that, in animals with MTL lesions, memory for well-learned, familiar stimuli would be spared relative to novel stimuli.

Consistent with this view, both perirhinal lesions (Eacott et al., 1994) and hippocampal disruption through fornix transection (Owen and Butler, 1981) disrupted performance of the DNMS task at short and long delays when large stimulus sets were used for testing. In contrast, minimal deficits were observed when a small set of highly familiar objects was used in testing. These findings suggest that medial temporal lesions may affect both WM and LTM for information that is complex and novel.

Based on these findings, one would expect human amnesics with large MTL lesions to exhibit impaired retention of complex, novel information across even short delays. We reviewed the extant literature and found several studies that investigated memory in amnesics using trial-unique DMS/DNMS paradigms similar to those used in primate studies (Squire et al., 1988; Aggleton et al., 1992; Holdstock et al., 1995; Owen et al., 1995; Buffalo et al., 1998; Aggleton, 2000). Results from these studies, shown in Figure 1, clearly demonstrate that patients with large MTL lesions exhibited deficits in retention of information across even short delays spanning a few seconds.

It should be noted that three of these studies summarized in Figure 1 reported data from amnesic groups that included patients with medial temporal damage and patients with diencephalic damage (Squire et al., 1988; Holdstock et al., 1995; Buffalo et al., 1998). Nonetheless, convergent results were reported from studies of patients with large MTL lesions following surgical resection (Owen et al., 1995) or herpes simplex encephalitis (Aggleton et al., 1992; Buffalo et al., 1998). Interestingly, the study by Aggleton et al. (Aggleton, 2000) did not observe deficits in humans with hippocampal disruption due to fornix damage. Structural MRIs from these patients, however, revealed that the hippocampal damage in the two of the patients with fornix lesions was incomplete, and the hippocampus in the third patients appeared grossly normal. Thus, the null effects observed by Aggleton et al. (2000) could reflect insufficient power to detect an effect. Alternatively, it is possible that, in patients with hippocampal disruption, surrounding cortical regions may be able to support working memory for novel information. Although it is unclear exactly why this would be the case, we will present computational analyses suggesting one possible explanation.

Neurophysiological and Neuroimaging Studies

Further evidence that these MTL regions may make contribute to short and long-term memory comes from single-unit recording studies of nonhuman primates. An advantage of this approach is that it allows the assessment of how and when MTL regions are recruited during memory tasks. For example, sustained neural firing during memory delays can be demonstrated

to be a neural correlate of active WM maintenance (Fuster and Alexander, 1971). Using DMS paradigms, several studies have reported such correlates of WM in perirhinal, entorhinal, and hippocampal regions (Watanabe and Niki, 1985; Miyashita and Chang, 1988; Cahusac et al., 1989; Nakamura et al., 1992; Miller et al., 1993; Colombo and Gross, 1994; Nakamura and Kubota, 1995; Fried et al., 1997; Suzuki et al., 1997; Colombo et al., 1998; Kreiman et al., 2000). Furthermore, analysis of the response properties of these regions suggests that their sustained responses may reflect maintenance of the type of information that is encoded by and represented within these regions.

For example, it is well established that neurons in the perirhinal cortex exhibit stimulus-selective responses to complex objects (Nakamura and Kubota, 1996). Studies using the DMS paradigm have demonstrated that these neurons also exhibit sustained, stimulus-specific firing during the delay period of the DMS task (Miyashita and Chang, 1988; Nakamura et al., 1992; Miller et al., 1993; Nakamura and Kubota, 1995). Furthermore, results suggest that this is not merely stimulus-driven activity, but instead reflects the active maintenance of a memory network. For example, one study found that object-specific delay activity of perirhinal and entorhinal neurons was retained only while the object remained relevant in the trial (Nakamura and Kubota, 1995).

In another set of studies, responses of perirhinal and entorhinal neurons were examined during the “ABBA” task—a variant of the DMS task that directly assessed responses related to object repetition and working memory (Miller et al., 1993; Suzuki et al., 1997). On each trial, a sample object was shown, followed by a variable number of test objects, and ending with the re-presentation of the sample. The monkey was rewarded for identifying the object that matched the sample. Because on some trials, foil test objects were repeated, the task required the active maintenance of the sample, rather than a mere judgment of the familiarity of the object. Importantly, neurons in both the perirhinal and the entorhinal cortex showed stimulus-specific sustained activity during the delay between the sample and the first test object. Furthermore, neurons in both of these regions exhibited enhanced responses to objects that matched the sample (“match enhancement”), but not to repeated foil objects. Analysis of trials following the first memory delay revealed an interesting dissociation—whereas perirhinal delay activity was terminated following presentation of a distracting foil item, entorhinal delay activity resumed following presentation of distracting items. Interestingly, analyses of dorsolateral prefrontal neurons on this task revealed a pattern of activity that was virtually identical to that seen in entorhinal neurons (Miller et al., 1996). In light of the anatomical interconnections between prefrontal, perirhinal, and entorhinal regions, these findings suggest that active maintenance of object information is supported by joint interactions between these regions. Indeed, computational simulations modeling such interactions revealed activity patterns in the model similar to those seen in the studies by Miller and colleagues (Renart et al., 2001).

Adding to this picture, studies by Miyashita and colleagues suggest that, rather than reflecting the activity of a passive WM buffer, perirhinal delay activity reflects the sustained activation of a long-term memory trace (Sakai and Miyashita, 1991; Naya et al., 1996; Naya et al., 2001). In these studies, monkeys learned to associate pairs of objects with one another. Next, a delayed paired-associate (DPA) test was administered, in which the monkey was shown one object and then required to choose the associated object after a brief delay. As noted earlier, numerous studies using the DMS task, perirhinal neurons exhibited delay-period activity selective to the remembered object (Watanabe and Niki, 1985; Miyashita and Chang, 1988; Nakamura et al., 1992; Miller et al., 1993; Nakamura and Kubota, 1995). However, the DPA task

is regarded as a long-term memory task, because the task requires the recall of an associated item that is not presented, rather than the maintenance of a presented item. Nonetheless, results showed that neurons showing object-selective delay activity in the DMS task also showed delay activity that was selective for the same object when its associate was presented as the sample (Sakai and Miyashita, 1991; Naya et al., 1996; Naya et al., 2001). These results, summarized in Figure 2, showed that perirhinal and entorhinal activity was similar whether a perceptual trace of an object was maintained in working memory or recalled from long-term memory. Consistent with the work of Miller and colleagues, further research has suggested that prefrontal, entorhinal, and perirhinal regions play a critical role in the initiation of the recall process (Rainer et al., 1999; Tomita et al., 1999; Naya et al., 2001; Rainer and Ranganath, in press). Collectively, these findings argue against the view that the MTLs solely support LTM. Instead, they are consistent with the view that these regions support WM by virtue of the information that they store (Fuster, 1995).

Remarkably consistent evidence has emerged from single-unit recording studies of the human hippocampus. Recording from microelectrodes placed in the MTL region in patients with severe seizure disorders, Fried and colleagues have examined MTL activity across a variety of memory tasks. In one study, these investigators reported that hippocampal and entorhinal neurons exhibited sustained firing over several seconds associated with the rehearsal of novel faces or objects (Fried et al., 1997). In another study, Kreiman and colleagues (Kreiman et al., 2000) recorded activity from medial temporal neurons during viewing of objects and during visual imagery for these objects. These investigators observed cells in the hippocampus and entorhinal cortex that responded during both visual stimulation and maintenance of a visual image in working memory. Remarkably, these investigators also observed that a significant proportion of cells that exhibited selective firing during presentation of certain types of visual stimuli also exhibited selective activity during active maintenance for these types of stimuli.

These neurophysiological data provide detailed information about the nature of coding by single neurons in the MTLs. Recent evidence from recent functional neuroimaging studies of human and nonhuman primates has revealed insights into the dynamics of MTL memory functions at a larger scale. For example, using 2-DG autoradiography techniques in monkeys, Goldman-Rakic and colleagues reported evidence for hippocampal, entorhinal, and perirhinal activation during the performance of DMS, as well as other WM tasks (Friedman and Goldman-Rakic, 1988; Sybirska et al., 2000; Davachi and Goldman-Rakic, 2001). Within the hippocampus, WM-related activity increases were greatest in the CA1 subfield, with modest activity increases also apparent in layers of the dentate gyrus and subiculum. Within the rhinal cortex, WM activity increases were greatest in lateral perirhinal cortex.

The advent of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) methods has allowed investigation of these issues in humans, albeit at lower spatial resolution. Interestingly, across all types of memory studies, activation of the hippocampus has been elusive, whereas activation of the posterior parahippocampal gyrus has been observed in several studies (Stern and Hasselmo, 1999). The infrequent occurrence of hippocampal activation may reflect the sparse nature of neural coding in this region (Stern and Hasselmo, 1999). Nonetheless, several groups have reported anterior hippocampal activity associated with working memory (Haxby et al., 1995; Eliot and Dolan, 1999; Curtis et al., 2000; Ranganath and D'Esposito, 2001; Stern et al., 2001). Furthermore, when complex, trial-unique stimuli were used, anterior hippocampal activation was consistently observed across three studies (Eliot and Dolan, 1999; Ranganath and D'Esposito, 2001; Stern et al., 2001).

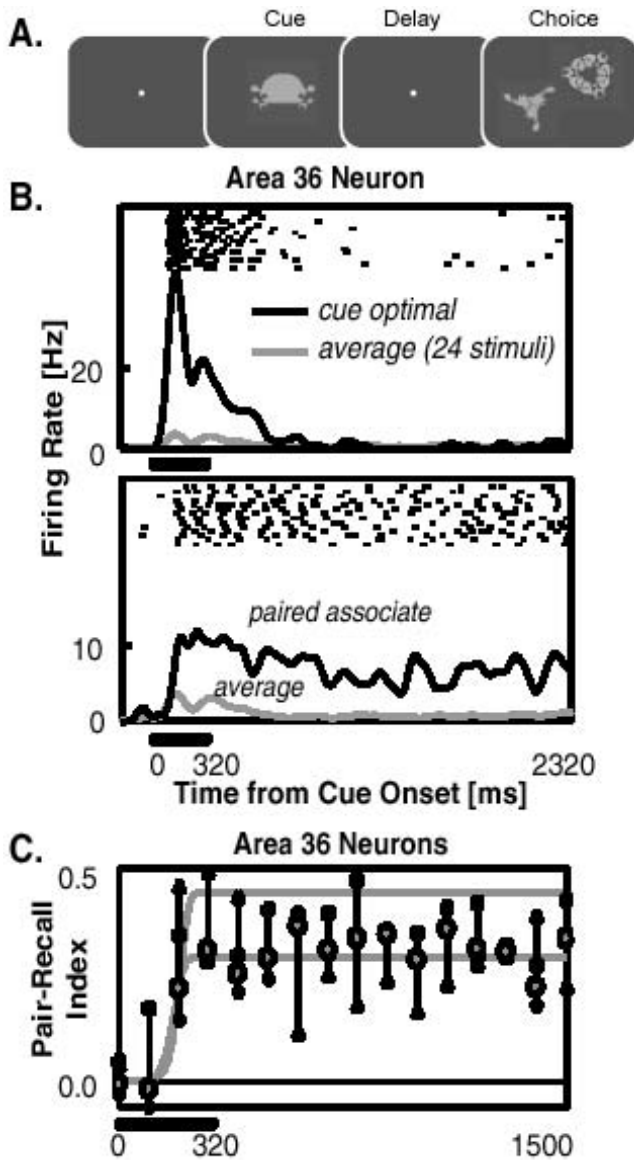


Figure 2. Neural activity in perirhinal cortex reflecting sustained activation of long-term memory networks. In this experiment, monkeys learned to associate pairs of fractal stimuli (Naya et al., 2001). A.) During recording, monkeys were shown one of the stimuli in each pair (“Cue”), and after a delay, they were shown the associated stimulus, along with a foil stimulus. Results from several studies suggest that, in this paradigm, monkeys recall the associated item during the delay period (Rainer et al., 1999; Miyashita and Hayashi, 2000). B.) In the top panel, activity is shown for one perirhinal neuron that exhibited selective responses for one of the learned stimuli. As shown in the top panel, this neuron showed transient increases in activity during the cue phase that were greater for the preferred stimulus (black line) than for other stimuli (gray line). Furthermore, when its associate was presented as the cue item, the neuron exhibited sustained firing that persisted across the delay period. Thus, activity in this neuron was correlated with the active recall and maintenance of this stimulus across the memory delay. C.) Responses from a population of visually responsive perirhinal cells to the paired associate of the preferred item. Note that these neurons exhibited sustained firing across the memory delay.

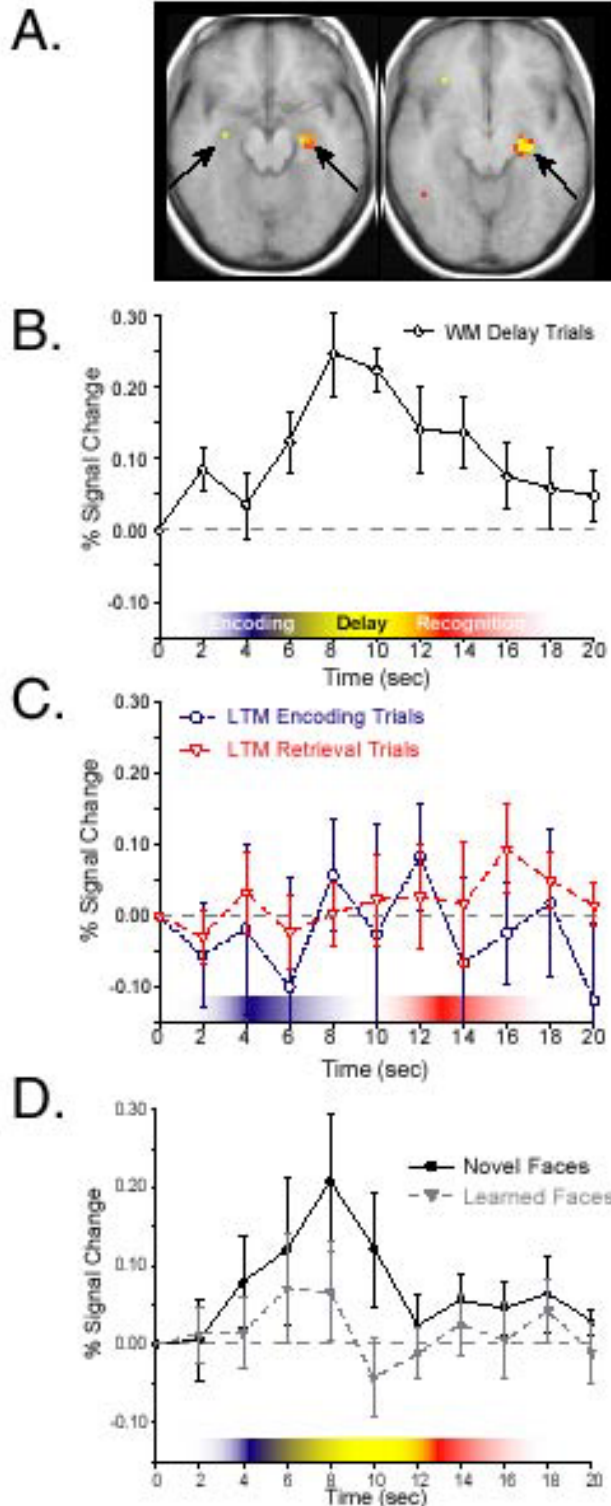


Figure 3. Human hippocampal activity associated with active maintenance of novel information. In this experiment, participants were scanned while performing a working memory task that required the active maintenance of a novel faces across a short delay period. A.) Results showed that bilateral regions in the hippocampus exhibited activation associated with the active maintenance of each face across the delay period. B.) Examination of trial-averaged responses in the right hippocampal region showed that this region exhibited sustained activity associated with WM maintenance. Note that in this figure, error bars denote the standard error of the mean across participants, and a color gradient shown in the background depicts when responses related to transient encoding (blue), sustained active maintenance (yellow), and transient retrieval (red) processes would be expected to peak. C.) Trial-averaged responses within this same region during LTM trials showed no reliable task-related signal changes. D.) In a second experiment, activity in the same right hippocampal region was compared between trials in which participants actively maintained novel versus familiar faces. Results showed that the right anterior hippocampal region exhibited greater delay period activity during novel than familiar WM trials. Thus, results from this experiment replicated the findings of the first experiment and extended them by demonstrating that the hippocampus is particularly engaged during working memory for novel information.

For example, in an fMRI study of trial-unique delay tasks, Eliot and Dolan (1999) observed that the hippocampus and perirhinal cortex were more active during blocks of trials with a 15s delay than during blocks of trials with a 5s delay. In another study reported by Stern

and colleagues (Stern et al., 2001), MTL activity was recorded during a “2-back” WM task with scenes as stimuli. In this task, which required constant maintenance and updating of the two most recently seen items, the hippocampus was more active during blocks of novel scenes than during blocks of familiar scenes. These results strongly suggest MTL involvement in WM for complex, novel information, but they leave open the possibility that activation may have reflected sensory, rather than mnemonic demands of the task.

Fortunately, the development of event-related fMRI methods has made it possible to analyze temporal patterns of activity within a trial (Zarahn et al., 1997; Postle et al., 2000; Zarahn, 2000). In a recent study, we used these methods to investigate the temporal dynamics of MTL activity during trial-unique delay tasks (Ranganath and D'Esposito, 2001). We used faces as stimuli in these experiments, because unfamiliar faces, like the object stimuli described earlier, are complex, and novel. In these experiments, activity was assessed during a WM task and during LTM encoding and recognition tasks.

On each WM trial, a sample face was shown and participants were asked to retain a mental image of the face over a 7s delay period. Next, a probe face was presented and participants decided whether it matched the sample face. In accord with prior neuropsychological studies, faces in the WM task were novel and trial-unique (Gaffan, 1974; Mishkin and Delacour, 1975). On each LTM encoding trial, one of a series of faces was shown, and participants were to learn them for a subsequent test. On each LTM recognition trial, participants saw a face and decided whether it matched one of the previously studied faces. Stimuli and temporal parameters of each trial were matched across WM and LTM trials, but whereas WM trials required the retention of a single face across a 7s delay, the LTM task required the retention of several faces across several minutes. Accordingly, this design allowed us to examine hippocampal activity during both WM and LTM tasks.

Results of this experiment showed that bilateral hippocampal regions exhibited sustained activity during the delay period of the WM task (Figure 3A, B). Activation was more extensive and larger in magnitude in the right than the left hippocampus. Further examination of right hippocampal activity during LTM trials revealed no reliable signal changes during LTM encoding and recognition trials (Figure 3C). In a follow-up experiment, activity during the same WM task was compared between trials in which faces were novel and trials in which faces were familiar. Results replicated the finding that the anterior hippocampus was active during the delay period for novel faces, and extended the finding by showing that delay activity was substantially more robust for novel than familiar faces (Figure 3D).

The findings from this study (Ranganath and D'Esposito, 2001) strongly suggest that hippocampal regions are robustly engaged during active maintenance of novel information. However, the lack of hippocampal activation during LTM encoding and recognition might seem unusual, considering that this region is thought to support long-term memory. Indeed, in light of the neurophysiological evidence showing hippocampal activity during stimulus encoding, maintenance, and recognition (Watanabe and Niki, 1985; Cahusac et al., 1989; Colombo and Gross, 1994; Fried et al., 1997; Colombo et al., 1998; Kreiman et al., 2000), it is likely that hippocampus is involved in these processes. Thus, we suggest that our neuroimaging findings (Ranganath and D'Esposito, 2001) reflect the nature of neural coding in the hippocampus. Specifically, the extant evidence suggests that transient stimulus-driven encoding and recognition engage the hippocampus, but that the resulting activity increase is relatively small, given the sparse nature of neural coding in this region (Stern and Hasselmo, 1999). However,

our results show that sustained recollection and maintenance of novel information over short delays can produce robust hippocampal activity. By this view, the same hippocampal mechanisms that enable recollection in the absence of bottom-up perceptual stimulation supported the active maintenance of novel faces in this study (Ranganath and D'Esposito, 2001). In the next section, we will present results of computational analyses explicating how hippocampal-cortical interactions may support encoding, maintenance, and retrieval of complex, novel information.

Computational Analyses: The SMRITI model

The evidence reviewed above suggests that, contrary to early views, the MTL make a significant contribution to short-term memory for complex, novel information. These findings then raise an important question: How are complexity and novelty related to the representation of information within MTL regions? Although the answers to this question are far from certain, computational analyses of medial temporal contributions to memory reveal important insights.

As discussed earlier, a wide array of neuropsychological and imaging data suggests that the hippocampal system (HS) (see Figure 4) consisting of the hippocampal formation (the hippocampus proper, the dentate gyrus, and the subiculum) and neighboring cortical areas in the MTL (the entorhinal, perirhinal, and parahippocampal cortices) plays an essential role in the encoding and recall of episodic memory (Cohen and Eichenbaum, 1995; Mishkin et al. 1997; Nadel and Moscovitch, 1997; Squire, 1992; Cohen et al., 1999; Dolan and Fletcher, 1999; Schacter et al., 1998; Schacter and Wagner, 1999). Many computational models of hippocampal function posit that the HS acts as an auto-associative memory (e.g., Marr, 1971; McNaughton & Morris, 1987; O'Reilly & McClelland, 1994; Treves & Rolls, 1994; Hasselmo et al. 1996) that can reconstruct a stored pattern in response to a partial or noisy version of the pattern. Another common view shared by many models is that the HS stores a conjunctive code that binds together the components of a memory (e.g., Marr, 1971; Halgren 1984; Squire, 1992; Alvarez & Squire, 1994; O'Reilly & McClelland, 1994; Murre, 1996; Moll & Miikkulainen, 1997). However, it is argued in (Shastri, 2002; 2001b,c) that the above view of HS function is inadequate for explaining the role of the HS in the memorization of events and situations. We summarize this argument below.

Reperesentational requirements of encoding events and situations

Consider an event *E1* where John gives Mary a book in the library on Tuesday. This event is an instance of a specific sort of interaction involving John, Mary and a book that occurs in a particular location (the library) at a particular time (Tuesday). John and Mary are performing specific “roles” in this interaction; John is doing the giving, and Mary the receiving. If this event were encoded using a conjunctive code by simply associating the concepts John, Mary, a Book, Library, Tuesday and *give*, the resulting encoding would be indistinguishable from that of an event where Mary gives John a book in the library on Tuesday. In order to make the necessary distinctions, the memory trace of such an event must encode bindings between the entities participating in the event and the specific roles they play in the event. For example, the encoding of event *E1* should specify the *role*-entity bindings: *giver*=John, *recipient*=Mary, *object*=a-book, *location*=Library, and *temporal-location*=Tuesday. Here, *giver*, *recipient*, *object*, *location*, and *temporal- location* are roles in the relational schema for the relation *give*, John and Mary are

different types of entities.³ Such an encoding involves two levels of bindings: (i) entities must be bound to the *roles* they fill in the event, and (ii) all role-entity bindings pertaining to the event must be grouped together to distinguish them from role-entity bindings of other events. This encoding is inherently more complex than a conjunctive representation.

Moreover, during retrieval, an episodic memory trace must be responsive to partial cues, but at the same time, it should be capable of distinguishing between the memorized event and other highly similar events. For example, the memory trace of *EI* should match the partial cue “John gave Mary a book,” but not the cue “John gave Susan a book in the library on Tuesday” even though the latter event is highly similar to *EI*.⁴ The requirement that an episodic memory trace must respond positively to partial cues, and at the same time, reject any cue that specifies an incompatible binding, entails that an episodic memory trace must be capable of detecting binding mismatches as well as binding matches (Shastri, 1999a).

Finally, during retrieval, an episodic memory trace should be capable of reinstating the event’s bindings within cortical circuits so as to recreate an active representation of the event. Cortical circuits encoding sensorimotor schemas and generic “knowledge” about actions such as “give” and entities such as “John”, “book”, “library”, and “Tuesday” can recreate the gestalt and details about *EI* upon being activated with the bindings associated with this event (Shastri and Ajjanagadde, 1993; Bailey et al. 1998; Barslouw, 1999; Lakoff and Johnson, 1999; MacWhinney, 1999).

It is argued in (Shastri 2002; 2001a-c) that in order to satisfy all of the above representational requirements, an event’s memory trace in the HS should be a complex relational structure incorporating neural circuits capable of (i) memorizing bindings (*binding-detectors*); (ii) detecting a mismatch between memorized bindings and bindings specified in a cue (*binding-error-detectors*); (iii) integrating the response of binding-error detectors (*binding-error-integrators*), (iv) detecting a match between a cue and the memorized event based on the response of abovementioned circuits (*relational-match-indicators*); and (v) reinstating the event’s bindings in cortical circuits in response to a matching cue (*binding-reinstators*).

Encoding relational memory traces via cortico-hippocampal interactions in SMRITI

The computational model, SMRITI⁵ (Shastri, 2001a-c; 2002), offers a circuit-level explanation of how a transient pattern of cortical activity encoding an event leads to the rapid formation of a functionally adequate relational memory trace in the HS. The model incorporates several anatomical and physiological properties of the HS, and proposes specific functional roles for each HS component and neighboring cortical areas in MTL. We review this model below because it explains some of the experimental findings reviewed above, and leads to several predictions about the role of the HS in episodic memory and working memory.

At a macroscopic level, the functioning of SMRITI may be described as follows. Our cognitive apparatus construes our experiences as a stream of events and situations. These construals are expressed as transient and distributed patterns of activity over high-level cortical

³ The encoding of an event may also require the specification of *parameter-values* of sensorimotor schemas. The problem of encoding parameter-value bindings, however, is similar to that of encoding role-filler bindings.

⁴ Given a cue, we may be reminded of a memorized event very similar to the cue. However, we become explicitly aware that there is a mismatch between the cue and the memory evoked by the cue.

⁵ *System for Memorizing Relational Instances from Transient Impulses.*

circuits (HLCCs). In turn, HLCCs, project to the entorhinal cortex (EC) and give rise to transient patterns of activity in the HS. This activity may correspond to the presentation of an event to the HS by HLCCs. Alternately, the activity arriving from HLCCs may correspond to a “query” to the HS, in which case the ensuing response of the HS corresponds to a response to the query.

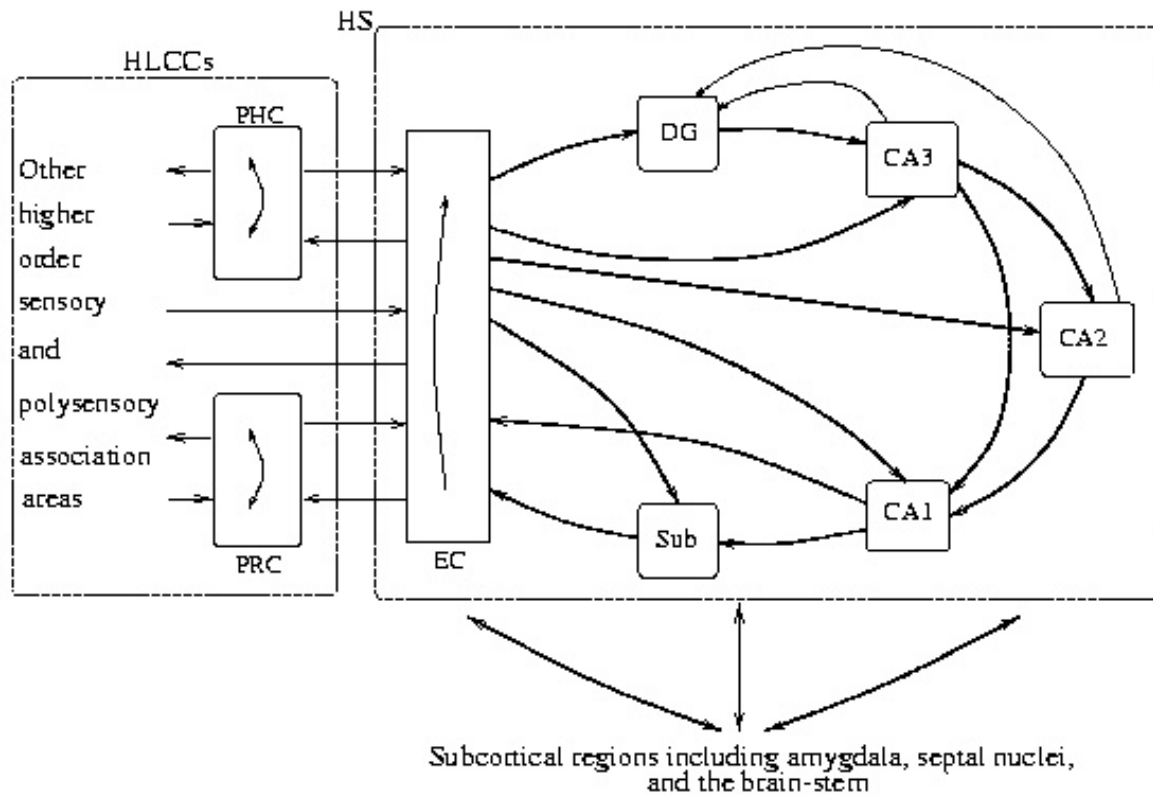


Figure 4. A schematic of the major pathways interconnecting components of the hippocampal system (HS) and the interactions between the HS and cortical and subcortical areas². The HS includes the entorhinal cortex (EC); the dentate gyrus (DG); Ammon's horn (hippocampus proper) consisting of fields CA1, CA2, and CA3; and the subiculum (Sub). EC is the principal portal between the HS and the cortex. Higher-order sensory and association areas project to EC directly or via the perirhinal (PRC) and parahippocampal (PHC) cortices. Activity converging on the HS courses through the complex loop formed by HS pathways, and returns to the cortical regions from where it originated. There also exist recurrent connections within DG, CA3, CA2, and to a lesser extent, within CA1. The HS contains a variety of inhibitory interneurons that together with principal cells form local inhibitory circuits. The HS also receives afferents from subcortical regions and projects back to many of these regions. Other cortical areas related to the HS are pre- and para-subiculum (not shown). (Reprinted from Shastri, 2002).

The transient activity injected into EC propagates around the complex loop consisting of EC, dentate gyrus (DG), fields CA3, CA2, and CA1 of the hippocampus proper, the subiculum (Sub) and EC, and triggers synaptic changes in these structures that lead to the formation of a relational memory trace. The activity arriving from CA1 and Sub into EC constitutes the

response of the HS. This reentrant activity propagates back to HLCCs and completes a cycle of cortico-hippocampal interaction.

Drawing on earlier work on neurally plausible representation and processing of relational information (Shastri and Ajjanagadde, 1993; Shastri, 1999b), SMRITI assumes that a relational schema (e.g., *buy*) is encoded in HLCCs by a collection of cell ensembles called a relational focal-cluster. The focal-cluster of a relational schema includes an ensemble of cells for each role of the relational schema. Entities (e.g., John) are also realized by focal-clusters in HLCCs. The structure of such entity focal-clusters is similar to (but simpler than) that of relational focal-clusters (Shastri, 1999b; Shastri 2001a,b). Dynamic role-entity bindings pertaining to an event are expressed by the transient synchronization of the bound role and entity ensembles (von der Malsburg, 1981; Shastri and Ajjanagadde, 1993; Singer and Gray, 1995; Hummel and Holyoak, 1997; Engel and Singer, 2001). Thus the dynamic encoding of “John bought Fido” consists of the John and Fido focal-clusters firing in synchrony with the *buyer* and *buy-object* role ensembles, respectively, in the *buy* focal-cluster. The grouping together of all dynamic role-entity bindings pertaining to a single event arises from the fact that all the role ensembles pertaining to a relational schema are components of the same focal-cluster. Thus an event’s relational structure is captured by the relative timing of activity within focal-clusters of the appropriate relational schemas and entities, and this transient form of relational coding is independent of the hippocampus.

Based on anatomical and functional considerations, SMRITI predicts that cell assemblies making up the focal-clusters of entities might be located in the anterolateral temporal lobe and ventromedial temporal cortex, but most likely, in the perirhinal cortex (PRC). SMRITI also suggests that cell assemblies making up the focal-clusters of relational schemas are located in (i) parahippocampal cortex which receives input from key cortical areas in the parietal and prefrontal areas, including prefrontal association areas 9 and 46 and (ii) other cortical areas projecting directly to EC. These hypotheses are consistent with findings that PRC plays a key role in encoding knowledge about entities (for a review see, Murray and Bussey, 1999), and PHC plays a role in encoding knowledge about the spatial layout of scenes (e.g., Epstein and Kanwisher, 1998; Epstein, Harris, Stanley, and Kanwisher, 1999).

SMRITI demonstrates that the propagation of rhythmic activity through the HS resulting from cortical activity described above can lead to the *rapid* formation of a relational memory trace. This memory trace is a complex neural circuit comprising of all the functional subunits, but the formation of this complex circuit is the natural consequence of the idiosyncratic architecture, local circuitry, and plasticity of the HS (Shastri, 2001b,c).

The relational memory trace formed in the HS consists of *linking* cells in EC for connecting HLCC-based focal-clusters to the HS; *binding-detector* cells in DG; *binding-error-detectors* circuits in CA3; *binding-error-integrator (bei)* cells in CA2; *relational-match-indicator* circuits in CA1; and *binding-reinstator* cells in the subiculum. Furthermore, *relational-match-indicator* circuits and *binding-reinstator* cells are connected to linking cells in EC.

In response to appropriate retrieval cues, activity within the HS reinstates the pattern of activity associated with an event in HLCCs, and thereby *recreates* activation-based representations of retrieved events in the cortex. Successful retrieval of HS-based relational memory traces is elicited by partial cues, but it is not elicited by similar (though erroneous) cues. The model predicts that the availability of a relational memory trace in the HS is essential for reinstating the relational structure of a retrieved event when the event is recalled from long-term

memory. Moreover, as argued below, the HS-based memory trace also plays a critical role in maintaining a relational event in working memory.

Predictions stemming from the SMRITI model

As discussed above, SMRITI proposes that (i) focal-clusters underlying cortical representations of entities are primarily encoded in PRC, (ii) focal-clusters of relational schemas are primarily encoded in PHC, and (iii) episodic memory traces of specific relational instances (e.g., episodes and trial-unique complex stimuli) are encoded in the HS, with EC being the locus of linking cells for connecting entity and relational focal-clusters to relational codes memorized in EC.

The ability of the HS to rapidly form memory traces suggests that it will automatically and rapidly become engaged in the representation of any significant event. Accordingly, SMRITI predicts that the HS will typically contribute to working memory function. In the case of simple events with minimal relational structure, this contribution would merely facilitate working memory function, but would not be essential. For example, working memory for simple verbal information could be supported by activating representations of phonological and semantic codes stored outside of the hippocampal region. In a similar vein, representations in PRC could be sufficient to support more complex memory processes, such as the formation of object-object associations and familiarity-based recognition (cf. Murray & Bussey, 1999).

However, because the hippocampus uniquely stores relational codes, we propose that in the case of novel, complex, and relational events, the contribution of the HS would become essential for the proper functioning of working memory. Specifically, SMRITI predicts that sustained hippocampal activity will be required for maintaining newly formed relational codes in an active state across short delays (i.e., in working memory).

The general prediction supported by computational modeling as well as from empirical data about the role of HS in WM function is as follows: feedback between prefrontal cortex (PFC) and PRC would suffice to maintain a simple object in WM. But a $PFC \leftrightarrow EC \leftrightarrow HF$ (i.e., $PFC \leftrightarrow HS$) loop would be required for maintaining a novel, complex relational object in WM.

Consistent with the above prediction, neuroimaging results described earlier (Ranganath and D'Esposito, 2001) show that the hippocampus exhibits sustained activity associated with the active maintenance of complex, novel objects (see Figure 3). Furthermore, SMRITI offers a potential explanation for why hippocampal activity reported by Ranganath & D'Esposito (Ranganath and D'Esposito, 2001) was greater for novel than for familiar objects. By this view, unlike highly familiar stimuli, novel stimuli are not likely to map to any pre-existing entity. If such stimuli are complex, such as the face stimuli used by Ranganath & D'Esposito, they would have to be expressed as a relational structure. Hence, PRC-based entity focal-clusters would not suffice, and PFC-HS interaction would be critical for the active maintenance of novel stimuli. The convergence of results from computational modeling and imaging studies leads us to propose that the HS is essential for maintaining novel complex and relational items in working memory.

The division of representational labor between the cortex and the HS proposed by SMRITI also helps explain the pattern of activity observed in the ABBA task (Miller et al., 1993; Miller et al., 1996; Suzuki et al., 1997) described earlier. During the performance of this task, PRC activity would consist of focal-cluster activity corresponding to the presented item. Because the task requires remembering item A -- even during the presentation of B -- the memory for "A

was the item presented first” would be encoded in the HS during the presentation of B, and this memory would be maintained in the active state by interaction between PFC and the HS (Miller et al., 1993; Suzuki et al., 1997).

Finally, SMRITI offers a possible explanation for why typical WM/STM tests are often insensitive to HS damage. Typically these tests involve stimuli such as words and objects that are both simple and familiar. As discussed earlier, cortical representations would suffice to encode these stimuli and the HS would not play a crucial role in the retention of this information over short intervals.

Conclusions

In conclusion, we have reviewed converging evidence from neuropsychological and neurophysiological studies to suggest that MTL regions may play a role in short and long-term memory. In particular, a vast body of evidence suggests that perirhinal and entorhinal neurons exhibit sustained activity during active maintenance of complex objects. Furthermore, combined lesions to these regions severely impair retention of complex novel objects across even short delays. At present, it is unclear whether perirhinal, parahippocampal, and entorhinal cortical regions may represent different types of information. Nonetheless, lesion and neurophysiological evidence clearly suggest that perirhinal and entorhinal regions support memory across short and long delays. Extant evidence suggests that the hippocampus also contributes to the retention of information across short and long delays, although selective hippocampal lesions appear to cause less severe short-term memory deficits than perirhinal lesions.

The SMRITI model reviewed above offers one set of plausible explanations for the different roles of PRC, PHC, and each HS component in the representation of complex relational stimuli. Furthermore, the model predicts that HS may be necessary for the retention of complex relational information across long as well as short delays. Further work using relational stimuli will be necessary to test the predictions made by the model

Although the nature of medial temporal contributions to memory will need to be investigated more thoroughly, the evidence we have reviewed suggests the need to reconsider the notion that short-term and long-term memory are neurally independent. As we noted at the outset, behavioral research on this issue in the 1960s was focused on differentiating between two alternatives—either that memory was supported by a single, undifferentiated long-term store, or that it was supported by two independent stores (LTM and STM). With the subsequent work on WM begun by Baddeley and colleagues (Baddeley, 1986), it became clear that neither of these alternatives was correct, and different stores were proposed to account for storage of different types of information (e.g., object, spatial, phonological, etc.). Recently, Baddeley (Baddeley, 2000) proposed an additional component to his model, called the “episodic buffer”, to account for short-term integration of complex, relational information.

In a similar vein, neurocognitive memory models proposed by Fuster (Fuster, 1995), Goldman-Rakic (Goldman-Rakic, 1987), Petrides (Petrides, 1989) and others (Squire, 1987; Eichenbaum and Cohen, 2001) and neurally motivated computational models (Shastri and Ajjanagadde, 1993) suggest that memories for different types of information (e.g., object, spatial, phonological, semantic, etc.) may have different cortical substrates. However, instead of proposing separate short-term stores or buffers for this information, these authors have suggested that short-term memory may reflect the temporary activation of multiple long-term memory

traces. By this view, working memory can be thought of as the activation of task-relevant long-term memory traces in the service of behavioral goals.

This view was expressed most eloquently by Fuster (1997): “*The evidence from the microelectrode and imaging studies is forcing us to re-evaluate the neural basis for short- and long-term memory, and to seriously question their structural separateness... Indeed, whatever its cortical distribution, one and the same network probably serves to store a long-term memory and to retain actively that memory for the short term.*” In light of the evidence reviewed in this article, this view of memory provides a neurally plausible account of the role of MTL regions in working memory, namely, the same MTL processes that support the representation and recall of certain types of information over the long-term, may also support the active maintenance of such information over short delays.

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