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The cognitive neuroscience of remote episodic, semantic and spatial memory

Morris Moscovitch[1], Lynn Nadel[2], Gordon Winocur[3], Asaf Gilboa[4] and R Shayna Rosenbaum[5]

The processes and mechanisms implicated in retention and retrieval of memories as they age is an enduring problem in cognitive neuroscience. Research from lesion and functional neuroimaging studies on remote episodic, semantic and spatial memory in humans is crucial for evaluating three theories of hippocampal and/or medial temporal lobe–neocortical interaction in memory retention and retrieval: cognitive map theory, standard consolidation theory and multiple trace theory. Each theory makes different predictions regarding first, the severity and extent of retrograde amnesia following lesions to some or all of the structures mentioned; second, the extent of activation of these structures to retrieval of memory across time; and third, the type of memory being retrieved. Each of these theories has strengths and weaknesses, and there are various unresolved issues. We propose a unified account based on multiple trace theory. This theory states that the hippocampus is needed for re-experiencing detailed episodic and spatial memories no matter how old they are, and that it contributes to the formation and assimilation of semantic memories and schematic spatial maps.

Addresses
[1] Department of Psychology, University of Toronto, 100 Saint George Street, Toronto, ON Canada, M5S 3G3, or Rotman Research Institute, Baycrest Centre, 3560 Bathurst Street, Toronto, Ontario, M6A 2E1, Canada
[2] Department of Psychology, University of Arizona, Tucson AZ, USA
[3] Rotman Research Institute, Baycrest Centre, Toronto, Canada
[4] Department of Psychology, University of Haifa, Mount Carmel, Israel
[5] Department of Psychology, York University, Toronto, Canada

Corresponding author: Moscovitch, Morris (momos@psych.utoronto.ca)

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Introduction

Memories used in everyday life are formed on the basis of information acquired recently and in the remote past, but most of our theories about the neurobiological basis of memory focus on information acquired in the laboratory in the not-too-distant past. Recently, however, the literature on remote memory has grown, and although it partly complements the findings from anterograde amnesia studies, it forces a re-evaluation of the theories that are based on them. Here, we highlight progress made in understanding the neural substrates that mediate remote memory, note the contribution recent studies make to neurobiological theories of memory, and discuss problems that need to be addressed in the future.

What is remote memory?

Remote memory begins with the creation of traces in long-term memory circuits, initially involving short-term processes completed within seconds, minutes or at most days [1••,2••]. Traces that outlast these initial stages form the basis of what we call here remote memory. Depending on the organism and the type of memory being considered, remote memory can represent events that occurred any time from a few days ago to decades earlier. One main question is whether remote memory depends on a process of prolonged or systems-level consolidation (see below and [3••,4•]); and if it does, how long does it take to complete? Additional questions include: is memory qualitatively transformed in the process, and what mechanisms are involved?

Problems in measurement of remote memory

If remote memories can last for decades in humans, studying them in the laboratory presents some obvious problems. Whereas the conditions for acquiring recent memory can be controlled, these must be relaxed or relinquished in studies of remote memory. Another problem concerns the ability to distinguish real memories from reconstruction, fabrication or confabulation [5,6]. To deal with these problems, many investigators have studied memories for which the time of acquisition, saliency, relative frequency of occurrence, and other related factors can be verified or estimated with some degree of confidence. These include memory for vocabulary, public events, personalities and facts about oneself, all of which fall in the realm of semantic memory (see glossary) and general knowledge [7]. These problems are not as easy to remedy when one examines memory for autobiographical events that are linked to a particular time and place, because these episodic memories (see glossary), by definition, are personal and much more difficult to verify [7].

Glossary

Allocentric: a kind of spatial representation that locates places in a framework external to, and independent of, the position of the observer.

Bound: Linked together in a neural or mental representation.

Episodic memory: Memory for specific events or episodes that one has experienced. It has two components: familiarity with the past event and recollection or re-experiencing of it.

Graded: Refers to memory loss that is sloped with respect to time of acquisition. Typically, memory loss is greater for recent than for remote memories.

Impulse response function: In event-related functional magnetic resonance imaging (fMRI,) the function describes the shape of a series of blood oxygenation level dependent (BOLD) 'impulses' or events, which reflect brief bursts of neural activity in response to stimuli.

Semantic memory: Memory for general knowledge about language, the world, and oneself.

Ungraded: Refers to memory loss which is equivalent across all time periods since acquisition.

Theories of hippocampal, medial temporal lobe and neocortical interactions in remote memory

Two major theories relevant to the neural underpinnings of remote memory, the cognitive map theory and the standard consolidation theory, make different predictions regarding hippocampal–neocortical interactions in remote memory. The newer multiple trace theory (MTT) offers yet another account [3••,4•,8–11].

All three theories agree that information registered initially in neocortex is integrated by the hippocampal complex–medial temporal lobes (HC–MTL) and related structures in the diencephalon (anterior thalamus and mammillary bodies) to form a memory trace that consists of an ensemble of bound (see glossary) hippocampal complex–neocortical neurons (see Box 1 for the names of structures comprising the MTL and their definition as used in this paper [12]). What happens after that, as new memories gradually become remote, differs among the three theories.

The 'cognitive map' (CM) theory posits that the hippocampus is needed to create allocentric (as opposed to egocentric; see glossary) spatial representations of the environment, and these representations provide the context in which episodic events are embedded [13,14]. Cognitive map theory does not distinguish between cognitive maps acquired recently and those acquired long ago, and hence the hippocampus should be important for retention and retrieval of both recent and remote spatial memories. Although it is not fully developed, the treatment of human memory hypothesized by the CM theory suggests that episodic, but not semantic, memory is mediated by the hippocampus, because spatial context is an integral part of episodes, whereas semantic memory is context-free [13,14]. Consequently, hippocampal damage should lead to impaired spatial memory no matter how long ago it was acquired, as well as impaired episodic retrieval (because spatial context is required for such retrieval), and hippocampal activation during retrieval of spatial memories should be independent of memory age. Presumably, the extent of hippocampal damage determines the severity of spatial or episodic memory impairment. Semantic memory, however, should be relatively spared.

Box 1

The hippocampal complex of the MTL includes: first, the hippocampal formation which comprises the hippocampus proper (CA fields), dentate gyrus and subiculum; and second, the adjacent regions of the MTL, which include the peri-rhinal, entorhinal, and parahippocampal cortices. In addition to the hippocampal complex, the MTL includes the amygdala.

According to the 'standard consolidation' (SC) model, there exists a process of prolonged or system consolidation [1•,2••] that could last months or even decades. During this process, the hippocampus (and possibly related diencephalic structures) is needed for storage and recovery of the memory trace. Hippocampal contribution diminishes, however, as consolidation proceeds until the neocortex, and other extrahippocampal structures, suffice to sustain the permanent memory trace and mediate its retrieval. Within the SC theory, no distinction is made between episodic and semantic memory. The very same memory trace initially mediated by the hippocampus whether episodic or semantic, is then mediated by brain regions that do not include the HC.

Because SC theory does not distinguish in a principled way among the various types of memory, it would predict that all memories become independent of the MTL over time, although the rate at which this happens might differ with frequency of occurrence. Thus, well-learned semantic and spatial memories might 'consolidate' sooner than less rehearsed episodic memories, but all memories consolidate in due course. Lesions of the MTL, therefore, should lead to a retrograde amnesia (RA), or amnesia for pre-lesion events, with a temporal gradient for all memories, and functional neuroimaging should show diminished MTL activation with time. Some proponents of SC have recently argued, however, that hippocampal activity is merely epiphenomenal to retrieval of remote memory, and does not reflect dependence of these memories on the hippocampus [15]. There are no predictions about the involvement of different MTL structures in remote memory nor about the relationship between lesion size and remote memory loss. SC theory predicts that damage that also includes lateral, neocortical structures can lead to temporally extensive RA for all types of memory.

Multiple trace theory (MTT) has its roots in both CM and SC, and in older literature on amnesia [16,17]. Similar to CM theory, it posits that autobiographical episodes are always mediated by the HC [3••,4•,18]. Indeed, the ability to re-experience or recollect the past in vivid detail

is considered a hallmark of hippocampal function [3••,4•,19–21]. According to MTT, each time an episodic memory is retrieved it is subsequently re-encoded, leading to formation of multiple traces mediated by ensembles of HC-neocortical neurons. Consequently, older episodic memories are distributed more widely in the HC than recent ones. The temporal extent and severity of RA for episodic memory, therefore, is related to the amount of HC damage. Semantic memory, however, benefits from HC contribution for a limited period after which it can be supported solely by neocortex. This applies to both verbal and spatial semantic memories [22]. According to MTT, cognitive maps of familiar environments are the spatial analogs of semantic memory: they are schematic, spatial representations enabling one to navigate in an environment but not necessarily to re-experience it in rich detail [3••,22,23]. As such, they can be mediated by extra-hippocampal structures in neocortex. Here, MTT clearly differs from CM theory. It also differs from SC theory in that MTT posits that as long as episodic memories retain their vividness and detail, they always will be dependent on the HC, no matter what their age. Some memories, however, are transformed with time, losing detail and retaining only the gist of the event, thus becoming more semantic or generic. Once transformed, such memories are no longer mediated by the HC, but can be mediated by neocortex.

According to MTT, MTL damage should lead to impaired episodic memory, the temporal extent and severity of RA being related to the age of the memory and the amount of damage, with very large lesions leading to a complete loss of detailed, episodic memories across the lifespan. Hippocampal damage in particular will affect the vividness of recollection and, conversely, vividness and personal significance will determine the extent of hippocampal activation. By contrast, semantic memory will be less affected by HC damage and can exist independently of it. Damage to the HC leads to relatively short RA for semantic memory, but damage to neocortex that is implicated in semantic memory leads to more prolonged RA, the extent and severity of which are determined by the age of the memory and the amount of damage.

MTT predicts graded (see glossary) RA as a function of lesion size and location in HC in two ways. First, older memories, having been retrieved and re-encoded more often, will be strengthened and/or more distributed in the HC in comparison with recent memories; hence larger lesions will be required to affect more remote memories. Second, because each structure in HC makes its own contribution to remote memory, and more of these structures are compromised as lesion size increases, minimal damage will tend to affect recent memories of one type (e.g. episodic), but greater damage will affect remote memories of more types (e.g. episodic and semantic). By contrast, SC theory has not addressed this issue with regard to HC explicitly, although presumably it could do so. At the moment, according to SC theory, time and frequency of occurrence are the determining factors in consolidating memories in neocortex.

As is evident, the three theories make different predictions with regards to both lesion and neuroimaging evidence. In reviewing the lesion literature in humans in 2000, Fujii *et al.* [24] observed that the findings, although not conclusive, mostly favored MTT over SC theory; they did not address CM theory. If the entire MTL was damaged, remote episodic memory loss was severe and extensive, even encompassing early childhood. As predicted by all theories, semantic memory loss, especially personal semantics, was temporally graded and extended to only about 10 years if damage was restricted to the hippocampal formation, but could be much longer if other regions of MTL and extra-MTL, neocortical structures were damaged. Fujii *et al.* [24] did not comment on remote spatial memory.

Here, we review the lesion and neuroimaging literature published since the Fujii *et al.* review. Until recently, little, if any, attention was paid to the relevance of studies of remote memory for cognitive map theory. Because there now are alternatives to the standard consolidation theory and because functional neuroimaging studies appeared only after the publication by Fujii *et al.*, the more recent studies address issues that help to distinguish among the theories, and the evidence that they adduce is more incisive. We focus on two inter-related questions that we believe are at the core of the differences among the theories. Although the structures that comprise the MTL, particularly the hippocampus, are central to these questions, this review will also touch on the contribution of other regions to remote memory.

First, is the HC equally implicated in retention and retrieval for all types of memory, including episodic, semantic, and spatial, across time? As a special case, do the vividness, details and personal significance of remembered events determine the extent of MTL involvement in retention and retrieval of remote memories in people who are neurologically intact?

Second, do the size and location of MTL and extra-MTL lesions determine the severity and extent of retrograde amnesia in patients with focal lesions? Conversely, does the age of the memory affect the amount of MTL and extra-MTL activation in people who are neurologically intact?

Lesion studies

Episodic memory

The evidence gathered since 2000 from studies of patients with focal lesions (see Table 1 and the more

Table 1

A list of all patients with focal lesions identified as single cases in the literature from 2000–2005, with location and extent of lesion, and performance on tests of remote memory

Study	Patient	Lesion			RA			
		H	HC	HC+	Episodic	Semantic		Spatial
						Personal	*General*	
Cipolotti *et al.* [28]	VC	B	l		UnGr	UnGr	UnGr, but intact familiarity	–
Haslam *et al.* [89]	TG	B	B	B	UnGr	Gr, approx 20 years	–	–
Van der Linden *et al.* [90]	AC	Lr	Lr	B	UnGr	Mild, Gr	Intact	–
Chan *et al.* [91]	NT	B	B	R	-	-	UnGr	–
Hirano *et al.* [29]	YK	B			UnGr	Intact	Intact	–
Grewal [92]	No initials	L	L	l	UnGr	Intact	40-year gradient	–
Rosenbaum *et al.* [53] (Remote spatial memory tested only at 20+ years)	KC	B	B	B	UnGr	Gr	Gr	Map intact; features impaired at 20+ years
Steinvorth *et al.* [25]	HM	B	B	B	UnGr except one event in adolescence	Gr	Mild, UnGr except adolescence	Remote map preserved (informal test [39])
	WR	Lr	Lr	B	UnGr	Intact	Intact except childhood period	–
McCarthy *et al.* [93]	RFR	B	B	R	UnGr	UnGr	Mild, familiarity intact	–
Bayley *et al.* [30]	AB	?	?	?	Gr	Gr	Gr[a]	–
(Gradients for episodic and personal semantic are difficult to assess because only memories from the first third of life were tested which were intact. We assume RA was graded)	JRW	B			Gr	Gr	Gr[b]	–
	RS	B			Gr	Gr	Gr[b]	–
	GW	B			Gr	Gr	Gr[b]	–
	LJ	B	b		Gr	Gr	Gr[a,b]	–
	MJ	b			Gr	Gr	Intact	–
	GP	B	B	b-B	Gr	Gr	Intact[c]	–
	EP	B	B	b-B?	Gr	Gr	UnGr for 40+ years	–
Stefanacci *et al.* [94] (remote spatial memory tested only at 40+ years)	EP (same as above)	B	B	b-B?	Gr (intact childhood and early adulthood)	Gr (intact childhood)	–	At 40+ years[d], remote map preserved
Bayley *et al.* [31•]	GT	B	B	B	UnGr	UnGr?	UnGr 40+ yrs[a]	–
	HC	B	B	B	Impaired	Impaired	–	–
	PH	B	B	l-L	UnGr	UnGr	–	–

Buchanan *et al.* [95] tested emotional autobiographical memory in patients with hippocampal damage of varying extents but did not report a time scale.

B, large bilateral lesion; b, small bilateral lesion; H, hippocampal formation; HC, hippocampal complex; HC+, lesions extending beyond HC to neocortex; Gr, (temporally) graded RA; L,R, side of large unilateral lesion; l,r, side of small unilateral lesion; RA, retrograde amnesia; UnGr, (temporally) ungraded RA; –, not tested.

[a] Includes tests from Reed and Squire [40].

[b] Includes tests from Manns *et al.* [32].

[c] Includes tests from Bayley *et al.* [31•].

[d] Includes tests from Teng and Squire [96].

detailed supplementary table) is largely consistent with the observations of Kopelman and Kapur, and Fujii *et al.* that are noted in their reviews [10,24]. When lesions are restricted to the hippocampus proper, RA is limited to a few years at most for episodic and semantic memory. When the lesion extends to the entire hippocampal formation, or to the adjacent regions of the MTL (hippocampal complex), two patterns can be discerned for episodic memory. One pattern that is consistent with the predictions of CM theory and MTT is derived from single case studies, including the case H.M. [25], from a number of different laboratories [26,27]. This pattern is that of a severe, temporally extensive and, for the most part, ungraded (see glossary) RA, which can encompass a lifetime in some cases [25–29]. The other pattern, consistent with SC theory, is derived from a series of patients studied in one laboratory [30,31•]. This pattern consists of intact episodic memory for autobiographical events at all time periods, if the damage is restricted primarily to the hippocampal formation, and a temporally graded RA with preservation of the most remote memories if the lesion encompasses the entire HC. If the damage significantly

affects other neocortical regions, particularly the lateral temporal cortex, then, consistent with all theories, RA is temporally extensive and ungraded.

This is especially the case for autobiographical memory, for which RA typically is noticeably more severe than for semantic memory. RA for semantic information usually seems restricted to a period of about 10 years if the damage is limited primarily to the hippocampal formation (but see [28]), but can be more extensive if the damage includes other MTL and neocortical structures, reaching the same level as autobiographical memory loss in the context of such extensive damage [24,32]. Similarly, decades-old spatial memories can survive large hippocampal lesions [22,33,34], although patients with lesions to extra-hippocampal regions typically activated in neuroimaging studies of remote spatial memory (see below) performed poorly on tests of allocentric spatial memory [34,35].

The evidence is clear that very large MTL lesions produce RA that extends for decades, which, by itself, speaks against a simple consolidation account because it is not biologically plausible for single memories to take so long to become permanent. A major point of contention, however, is whether episodic, autobiographical memory from the most remote time periods, usually childhood and early adulthood, is preserved or impaired when damage is limited to the MTL. Another issue is whether damage limited to the hippocampal formation can produce temporally extensive RA at all. Functional and anatomical reasons have been offered to account for the discrepancies among studies, but it is difficult to see how the issue can be resolved without further investigation. According to the functional account, it is the recollective quality and detail of the remembered event that is the hallmark of episodic memory and hippocampal involvement. Because most autobiographical memories lose their vividness (detail) as they age [36], memories of amnesic and healthy people might appear equally impoverished at remote periods if memory is queried insufficiently. The autobiographical memory interview [37], a standard test of remote episodic and semantic personal memory that is used in most studies (see supplementary table), is adequate for revealing differences between controls and amnesics in most cases. In other cases, however, special interviewing and scoring procedures might be needed [25]. Thus, such tests have revealed extensive memory loss dating back to early life, even in the patient H.M. [25], although on less sensitive tests his RA appeared more limited [38,39]. Bayley *et al.* [30,31•] also used more sensitive tests, but still reported no difference at the most remote time period between amnesics with large MTL lesions and controls. Differences in testing procedure and scoring might account for discrepancies in the results. It should also be noted that one of their patients, E.P., who had lesions primarily to the hippocampal formation or complex and intact memory for very remote autobiographical events, had ungraded deficits in semantic memory (lasting at least 40 years) [40].

By contrast, the anatomical account attributes the difference between extensive and temporally limited RA to lesion size and location. Drawing on carefully documented neuroanatomical analysis of a series of amnesic patients, Bayley *et al.* conclude that RA encompassing the earliest periods of life is found only in patients whose damage extends beyond the MTL to regions of neocortex [30,31•]. In their view, damage that is confined to the MTL spares memories for the most remote periods. Other cases, however, with lesions confined to the MTL, or even the hippocampal formation (see Table 1 and supplementary table), show RA across the lifespan. At least one of those cases, V.C., is as well-documented neuroanatomically as the cases in the Bayley *et al.* series [28] and, except for memory loss, is at least as cognitively intact.

Thus, both the functional and the anatomical accounts of the discrepancies in the literature are found wanting. There are reports of ostensibly vivid, remote memories being spared [30,31•], and there are cases with damage limited to the HC or MTL that show impaired memory even at the most remote periods [3••,4•,28]. For the same reasons, other issues also are unresolved, including the extent and nature of focal RA, of transient global amnesia, of the correlation between lesion size and extent of deficit [10,27,41], the unique contribution, if any, of the different regions of the HC, and of memory loss following different types of dementia [42,43,44]. Although we believe that on balance the evidence favors MTT, we are aware that some of the studies are inconclusive, and others are open to different interpretations. Clearly, more research is needed before one of the models is supported conclusively.

Semantic memory

In contrast to the controversy surrounding episodic memory, there is little dispute about semantic memory. Consistent with all three theories, RA for semantic information, whether it is for facts about oneself, about public events, personalities, or even vocabulary (see supplementary table), is either spared or confined to a period of about 10 years if the damage is limited primarily to the hippocampal formation (but see [28]). RA can be more extensive if the damage includes other MTL and neocortical structures, reaching the same level as autobiographical memory loss given such damage, or even exceeding it in the case of patients from the Bayley *et al.* series [24,32]. In a cross-sectional and longitudinal study of semantic memory for famous names and vocabulary in patients with Alzheimer's dementia (AD), Westmacott *et al.* [45] showed that the extent and severity of RA increased with disease progression, suggesting that RA for semantic memory is related to the extent of neocortical atrophy.

Spatial memory

Although the hippocampus is needed for acquisition of allocentric spatial information, very remote, spatial memories can survive large hippocampal lesions [22,33,34]. MTL damage that does not include parahippocampal cortex fails to impair spatial memory for long-familiar environments. Patients with such lesions can navigate normally in these environments and perform well on a variety of tests of spatial memory on those environments (for tests, see section on neuroimaging). By contrast, patients are impaired in navigation on such tests if they have lesions to extra-hippocampal regions such as the parietal, parahippocampal and posterior cingulate or retrosplenial cortex, each of which contributes to different aspects of spatial memory and navigation (Figure 1) [35]. Many of these structures have reciprocal, anatomical connections with each other and with the hippocampus [46–50], forming a spatial network (Figure 1). The hippocampus might be needed to bind information from these spatial networks with information from other sources, to form the richly detailed memory representations underlying one's ability to re-experience recent or remote events [3••].

Such findings argue against one aspect of CM theory but are consistent with SC theory and MTT, both of which predict that remote spatial memories should survive hippocampal damage. The implications of these findings are discussed after the neuroimaging evidence is presented.

Damage to extra-MTL structures, such as pre-frontal cortex, basal forebrain, and diencephalons, can also lead to extensive, and often temporally graded, RA [10,51,52]. Because remote memory in people with these lesions has not been studied as thoroughly, it is not yet known whether the RA is related to loss of memory, to impaired retrieval, or to both.

In summary, damage restricted to the MTL produces a temporally graded RA for semantic and episodic memory, with the latter typically being more severe and extensive, sometimes lasting decades according to one view, or to an ungraded episodic memory loss according to another. There is least agreement as to whether the most remote episodic memories are spared or lost following extensive MTL lesions, with proponents of both CM theory and MTT arguing that vivid, detailed recollections are impaired for the entire lifetime, and proponents of SC theory arguing that such loss occurs only if the lesions extend beyond MTL to neocortex. RA for allocentric, spatial memory resembles semantic memory, in that only the more recent memories are affected following MTL lesions, thereby supporting MTT and SC theory, but not

Figure 1

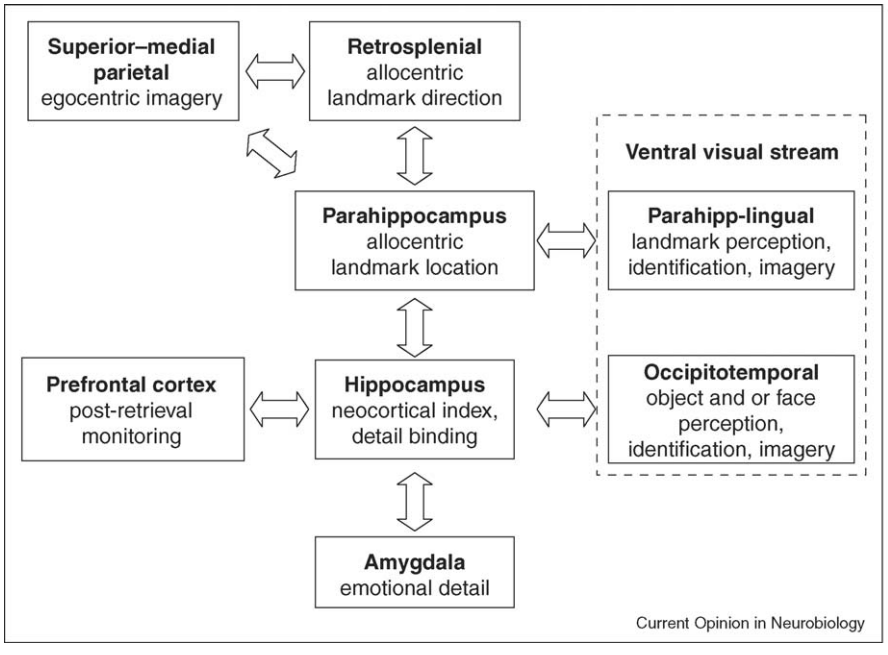

Illustration of a hippocampal–neocortical framework of episodic and spatial memory. The arrows connecting regions via the parahippocampus represent an example of a subnetwork of structures supporting one class of schematic information (spatial) that has been abstracted over time and that can exist independently of the hippocampus. The remaining arrows represent connections between the hippocampus and the specialized neocortical regions that enable the reconstruction in memory of newly formed traces and of event-specific details. Together, the network, with the hippocampus as its hub, can represent details of events in a spatial context [3••].

CM theory. Like semantic memory, remote spatial memory sufficient for navigation is represented in extra-hippocampal structures.

Functional neuroimaging

Lesion data tell us how the individual copes with damage to a particular brain region. They cannot tell us what that region would be doing if it were intact. Lesions also do not respect the boundaries of interest to researchers, which places an unreasonable premium on those rare cases that seem to be 'pure', however unattainable such cases might be [53]. The advent of functional neuroimaging methods [54] makes it possible to address this issue more directly, and to assess other predictions of the three theories in healthy neurologically intact people. Such converging evidence might help in ascertaining which of the theories, if any, is on the right track.

Episodic memory

The majority of neuroimaging studies of autobiographical (episodic) memory report that in the MTL there is equivalent activation to retrieval of recent and remote episodic memory, especially in the hippocampus, as predicted by both the CM theory and MTT. This pattern of activation is obtained in positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) regardless of the interval, which varies from days [55,56] and weeks [57] to decades [58], or the particular procedures used to elicit and test autobiographical memories: for example, recognition of sentences describing events [55,59,60,61] and re-experiencing events in response to cue words [58,62–65], generic sentences [55] and family photos [66•]. Activation is typically seen in left and/or right hippocampus when these episodic memory retrieval tasks are compared with various baseline tasks (e.g., reading simple sentences or sentences describing personal semantics or public events, completing sentences, or viewing photographs), with different studies showing different patterns of lateralized activation. Even in an individual with hippocampal lesions who was amnesic from early childhood, activation of residual hippocampal tissue was found only for the very few, remote episodic memories that he had [60]. Although it is possible that all these results reflect hippocampal activation associated with re-encoding of memories retrieved in the scanner, a number of controls suggest that this is not the case. First, such hippocampal activations are not obtained for semantic or generic memories retrieved in the scanner, which would presumably also be re-encoded [55,59,60,61]. Second, the same pattern of hippocampal activation during retrieval is found even when the baseline (or comparison) event involves generating a detailed imaginary scenario of an event that participants never experienced [66•]. In this study, although hippocampal activations were equivalent for vivid recent and remote memories, they were distributed differently in these two conditions. Activations associated with recent memories clustered at the anterior end of the hippocampus, those associated with remote memories were distributed throughout its length.

A few studies show a temporal gradient of activation in the hippocampus [67,68], but in these studies there was no control for either vividness, number of details or personal significance [69], or no effort was made to determine the contribution of these variables, of which the former two are known to vary inversely with the age of the memory. Eustache *et al.* [70] note that older memories are typically sketchier and more semantic than recent ones. In addition, Addis *et al.* [64] have shown that hippocampal activation is modulated by vividness, emotionality and personal significance; memories that rated high on those qualities in the scanner led to greater hippocampal activation. Although the recency of memories modulated hippocampal activity, its effects were reduced or eliminated when the above experiential factors were included as covariates. Conversely, robust modulation of hippocampal activation was observed for the three experiential qualities even when recency was included as a covariate [63]. Taken together, these studies are consistent with predictions formed on the basis of the CM theory or the MTT, but not the SC theory.

The only exception with regard to recency is a study by Maguire and Frith [61], in which they found a temporal gradient of activation in the right hippocampus in older, but not in younger, adults. The cause of this anomaly is not apparent, but one possibility is that it takes longer to recover remote memories than recent ones, especially in the elderly, and that the time course to do so is greater in the right hemisphere [58,71,72]. Because of the brief scanning time, it might be that the full amount of information represented in the right hemisphere was not recovered for the most remote memories.

In addition to the MTL, many other brain regions are implicated in retrieval of autobiographical memories. These areas form a primarily medial and left-lateralized cortical and subcortical network that has the hippocampus as its hub and includes medial and ventrolateral frontal cortex, medial and lateral temporal lobes, temporo–parietal junction, retrosplenial and posterior cingulate cortex, cerebellum and thalamus [59]. Because the specific contributions of these regions have not been examined systematically in tests of remote memory [63–65], we do not speculate about their function here [3••,72,73,74•]. What is worth noting, however, is that although the activation in some of these regions is sensitive to the age of the memory, it is almost always the case that the activation is stronger to recent than to remote memories. This result is in the opposite direction to that predicted by SC theory, which posits that the more remote memories are the ones that should be cortically mediated.

At the present time, the neuroimaging evidence regarding episodic memory favors both CM theory and MTT. Consistent with the major tenets of these theories, hippocampal activation to retrieval of autobiographical episodic memories did not vary with the age of the memory, no matter how remote it was, but did vary with the experiential quality of the memory, and the more vivid and personally significant the memory, the greater the activation. Investigations into the contributions of different regions of MTL and of extra-MTL structures to remote memory are just beginning.

Semantic memory

The neuroimaging evidence on semantic memory is less consistent than that on episodic memory. There have been fewer studies examining remote memory for personal semantics or public knowledge of people and events. Those that have been conducted report various effects: no hippocampal activation; hippocampal activation but without a gradient for personal semantics, knowledge of public events [59] or famous faces [75–77]; or a temporally graded activation in right entorhinal cortex to famous faces [78] and in right parahippocampal cortex to famous names [71]. In all cases, the time range sampled was greater than 20 years, and extended as long as 50 years [78]. The source of the discrepancy is difficult to determine. One possibility is that some semantic memories might be associated with an episodic component that influences the type of activation observed [45,79], such that the episodic component is mediated by the left hemisphere and the more semantic component by the right. This possibility is considered in a recent, carefully controlled fMRI study examining recognition of names of famous people by Douville *et al.* [71]. In examining the impulse response function (see glossary), they found greater hippocampal and parahippocampal gyrus activation to famous names than that to distractors, with a temporal gradient for the right but not left parahippocampal region. These results resemble those reported by Maguire and Frith [61] for autobiographical memory in elderly people. Thus, another interpretation is that the left-sided activations reflect participants' autobiographical associations (episodic memory) with the famous names. The right-sided activations might reflect recovery of the details of the experience [72]. The study by Bernard *et al.* [77] on famous faces also confirms that hippocampal activation without a gradient is not the result of re-encoding old stimuli, because encoding new faces is associated with anterior hippocampal activation, whereas retrieval of familiar faces is associated with posterior activation.

The temporal gradient observed in some studies of semantic memory is consistent with CM theory, MTT and SC theory, in that they all predict that hippocampal involvement in retention and retrieval of semantic memory diminishes with time. Reports of the absence of a temporal gradient favor the CM theory and the MTT, in that they might reflect the contribution of an episodic component.

Spatial memory

There are only a handful of functional neuroimaging studies on remote spatial memory. Maguire *et al.* [80] tested the ability of experienced London taxi-drivers to find new routes from one location to another when familiar routes were blocked. They report hippocampal activation associated with success in novel pathfinding, but the region of activation is in the parahippocampal cortex, not in the hippocampus itself. Similarly, in a test that required participants to re-experience an event in a particular location (combined spatial and autobiographical memory test), Niki and Luo [81] found greater activation in the left parahippocampal gyrus when contrasting recent (within two years), detailed events with remote (seven years), detailed events. Mayes *et al.* [82] conducted a complex study contrasting different types of spatial, semantic and episodic memory, acquired either recently (within weeks as most) or four years earlier. They found activation in the right body and head of the hippocampus when contrasting the reliving of an episode in a particular place (static episode) with recalling the location of six towns on a map (semantic spatial), with no effect of age of the memory. The hippocampal activation might be related to the spatial nature of the memory, or to the vividness and number of details of the environment and autobiographical context of the experience, similar to that found for hippocampal activation of episodic memory (see above). In both of the studies, however, there also was activation in parietal, parahippocampal, posterior cingulate cortex and precuneus, all structures that are part of a spatial network (Figure 1).

To examine remote spatial memory, Rosenbaum *et al.* [83•] used a version of the Toronto public places test (TPPT), modified for scanning. They tested participants' spatial knowledge of the downtown core of Toronto (about a two square miles) on a variety of mental navigation tasks including vector mapping, distance and proximity judgements, and blocked routes. They found that, contrary to the predictions of the CM theory, the hippocampus proper was not activated on any of the tests more than it was on the baseline control task, although the parahippocampal cortex was active, as noted by Maguire *et al.* [80]. Instead, the level of activation in extra-hippocampal regions varied with the particular demands of each task. For example, the superior-medial parietal cortex was implicated more in egocentric tests of spatial memory, such as landmark sequencing, whereas the retrosplenial cortex was implicated more on allocentric tests, such as vector mapping, distance judgments and proximity judgments. Memory for familiar places activates some of the same regions and also parts of anterior temporal cortex [84] (Figure 1). The only evidence of hippocampal

activation to familiar places comes from studies in which there is some personal, spatial reasoning [81,85,86], suggesting that the experiential component is crucial.

The neuroimaging evidence on remote spatial memory, similar to the lesion evidence, challenges a basic tenet of the CM theory that the hippocampus represents allocentric spatial information, no matter how long ago it was acquired. Instead, the findings favor MTT and the SC theory, both of which claim, for different reasons, that remote spatial memories can exist independently of the hippocampus. Thus, although the CM theory predicted that the hippocampus would be implicated in episodic memory because of its spatial context, the evidence from both lesion and neuroimaging studies on remote spatial memory raises the possibility that the converse might be the case; spatial memory is mediated by the hippocampus because it is part of an episodic memory or experience. As we suggest below, however, the possibility remains that the remote spatial memories existing independently of the hippocampus are coarser than those that depend on the hippocampus. If this proves to be the case, the CM theory would remain viable with regard to its treatment of remote spatial memory.

Summary

The functional neuroimaging studies show that with respect to memory for autobiographical episodes and space, the factor determining hippocampal complex activation is the quality of the recollective experience — its vividness, emotionality and personal significance — and not the age of the memory or its spatial aspects. Such evidence favors primarily MTT, although evidence of a temporal gradient in a few studies leaves open the possibility that the SC theory is still viable. Memories of personal facts, public events and famous people have an inconsistent effect on activation of the hippocampus and related MTL structures, with evidence of a temporal gradient in some studies, as all theories predicted, and no gradient in others, perhaps reflecting an added, episodic component. Retrieval of spatial maps formed in the remote past does not seem to activate the hippocampus more than control tasks, calling into question a basic tenet of the CM theory.

Conclusions and a theoretical proposal

The evidence reviewed here suggests that an episodic–semantic distinction can be applied to both spatial and nonspatial memory, and thus provides a unified framework for conceptualizing hippocampal– neocortical interactions [3••,4•,23]. In this framework, detailed representations of remote events (episodic, autobiographical memory in humans [3••,4•] and context-dependent memory in animals [23]), including rich spatial representations of environments, are hippocampus-dependent, whereas semantic memories (context-free memories) and schematic or coarse representations of the topography (sufficient to support navigation) can exist independently of the hippocampus.

Hippocampal traces provide an index to regions of neocortex where the details of one's life experiences are stored. Each hippocampal trace, that is, each index, binds an appropriate set of neocortical traces into a representation that enables one to re-experience a particular event with many of its details, including the environment in which it occurred. In many ways, the theoretical position espoused for the role of the hippocampus in remote memory is congruent with the emerging view of the hippocampus in recent (anterograde) memory in humans and other animals; it is needed to represent information that supports recollection of the past, but not context-independent familiarity with it [19–21,87,88]. Insofar as memories reflect detailed information, they will continue to be dependent on the hippocampus. Memories, however, are typically transformed with time, losing details and becoming more schematic. What is more, retrieval appears to re-instantiate a previously stored and consolidated memory, which can then be transformed by the subsequent retrieval context [1••,2••]. We suggest that describing and tracking these transformations, and not simply the time course of consolidation, will enhance our understanding of which structures mediate memory over time and to what effect.

Update

Since completing the paper, these additional articles have come to our attention [97–100]. They complement the findings reported in this paper and, except for the review by Spiers *et al.*, are consistent with the view that the hippocampus is needed to mediate remote autobiographical, but not semantic, memory.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.conb.2006.03.013.

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