Systems consolidation and hippocampus: two views

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Abstract Two approaches to systems-level memory consolidation are contrasted. The standard model and multiple trace theory are spelled out, their implications are outlined, and their fit to the data from a number of approaches is evaluated. We conclude that the data from neuroimaging studies strongly support multiple trace theory, that data from neuropsychological studies favor but does not conclusively support multiple trace theory, while evidence from a new approach, the study of prospective memory, also supporting multiple trace theory, offers a promising new way to distinguish between these two theories. Work with animals is largely consistent with this conclusion. We suggest that the hippocampal and neocortical systems are critical for different forms of memory, and that the shift of memory from dependence on hippocampus to dependence on neocortex during consolidation is a reflection of the fact that memory often is transformed with time, becoming more generic in nature. Insofar as detailed episodic recollections are retained, the data show that they are dependent on the hippocampal system, much as multiple trace theory postulated.

The idea that memories are "consolidated" at the systems level emerged about 60 years ago from two key findings: Russell and Nathan [73] showed that the retrograde amnesia (RA) resulting from brain trauma can last days or even months, and Scoville and Milner [77] showed that resection of the hippocampus apparently caused both anterograde amnesia and RA, the latter lasting as long as several years. Because it was thought that the short-term (STM) and long-term memory (LTM) capacities of the patient H.M. were intact, it was concluded that parts of the medial temporal lobe (MTL) played some critical, although unspecified, role in transferring memories from STM to LTM. Interest focused quite soon on the hippocampus within the MTL (see [65]).

For some time this notion of transfer was taken literally; it was assumed that a given memory was initially "stored" in hippocampal circuits, and then somehow transferred or reestablished in extrahippocampal (likely neocortical) memory sites. Perhaps the first statement of this position was contained in Marr's [44] model of the hippocampal system. The more general idea that systems consolidation (or prolonged consolidation, compared to synaptic [Dudai 2004] or rapid consolidation [Moscovitch 2000] involved long-term interactions between hippocampal and extrahippocampal circuits was expressed in an article by Squire et al. [79]. The "standard model of memory consolidation" (henceforth SMC) emerged from these writings. It is important to note at the outset that this model was originally intended to apply to explicit forms of memory,

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including both episodic and semantic memory,[1] although these terms were not in use in the 1950s and 1960s (see [60] for a recent discussion of the emergence of ideas about multiple memory systems). The fact that early discussion of systems consolidation concerned only one type of memory is important in understanding the theories that emerged and their limitations. More recently it has become clear that systems-level consolidation, understood as interactions between multiple brain systems influencing LTM storage, might be occurring also for implicit forms of memory, but in this case the relevant structures are other than the hippocampus and its neighbors in the MTL.[2] Our focus here will be on explicit memories and the standard model offered to explain how these kinds of memories are consolidated, because this is really what the historical debate is all about. It will be interesting in the future to ask whether the principles that apply to systems consolidation in explicit memory are also relevant for implicit memory.

The standard model supposes that the hippocampus plays a time-limited role in memory storage, either by first storing and then transferring a memory, or by acting as an index (cf. [83] for an early formulation of this indexing idea) that binds extrahippocampal storage sites during a period when direct communication among these sites is inadequate to permit memory retrieval. As a function of replay, either during rehearsal or offline, these extrahippocampal sites acquire the ability to interact such that the hippocampus is no longer needed to retrieve the memory. Initially a supporting argument held that there is limited capacity within hippocampal circuits, creating a need to recycle hippocampal neurons back into a pool of available

elements for new memory formation (e.g., [3]). When extrahippocampal sites can interact to retrieve memories, the hippocampus is no longer needed and systems-level memory consolidation is said to be complete. Before this time normal memory retrieval requires hippocampal involvement. Within this model little was said about the time course of changes in the strength of memory representations in hippocampal and extrahippocampal circuits. Is it because the former is weakening even as the latter is strengthening? If so, how could they still support retrieval? If not, are hippocampal traces suddenly erased just when extrahippocampal traces reached coherency? Or does the hippocampus continue to contribute as it did before consolidation, but in a way that is complementary rather than necessary? Questions of this kind were rarely, if ever, asked.

Notwithstanding the lack of the kind of details just noted, SMC gained rapid acceptance in the field (cf. [78]), entering the textbooks as a fact about memory and the brain. Questions about this approach came from researchers working both with humans (e.g., [88–90]; Kinsbourne and Wood 1975) and with animal models (e.g., [38]), but their concerns were not considered sufficient to challenge the main ideas expressed in the standard view. One frequently sees uncritical acceptance of SMC in both the scientific and nonscientific literature—the hippocampus, in this view, is only important for memory for a brief interlude.

A challenge to the standard theory

About 10 years ago we began to question SMC seriously [51, 61, 62]. Based on a comprehensive review of the existing literature we concluded that SMC suffered from quite serious problems. Some of these were empirical, whereas others were conceptual, and several were severe enough to cast doubt on SMC.

Problems with SMC

The problems with SMS are as follows:

1. The apparent extent of RA, hence the length of the consolidation period, varies with both the memory task being tested and the method used to produce amnesia, e.g., lesions, electroconvulsive shock, immersion in cold water, or the injection of protein synthesis inhibitors. To complicate matters further, the animal literature measures consolidation in hours, days, or weeks at most, whereas the human neuropsychological literature measures consolidation in years, if not decades.
2. Insofar as one imagines a transfer of memory from hippocampal to extrahippocampal sites, no empirically

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[1] There is considerable disagreement about which terms to use in referring to various kinds of memory. Whereas episodic and semantic memory are relatively well defined, the umbrella terms embracing both of these, explicit or declarative memory, are each fraught with difficulty. The former, with its partner implicit memory, was introduced not as the name for a memory system, but rather as a description of the methods used to assess it. The latter, with its original partner procedural memory, was introduced as a name for a memory system, but it has proven virtually impossible to define in a noncircular way. We prefer the theory-neutral nature of the terms "explicit" and "implicit," while acknowledging that explicit memory is not a "system."

[2] The terminology for MTL structures is not consistent in the literature. Here, the hippocampus proper refers to the cornu ammonis fields and dentate gyrus. The hippocampal formation includes the hippocampus proper and the subiculum, whereas the hippocampal complex includes the hippocampal formation plus entorhinal and perirhinal cortex, and the parahippocampal cortex. Both SMC and MTT discuss consolidation with respect to the hippocampus proper. Whereas proponents of both theories recognize the importance of other MTL structures in memory encoding and retrieval, neither theory makes strong claims regarding the specific roles these structures may play, or how they interact with one another.

supported mechanism to accomplish this has been offered. If one imagines that memory is always stored in extrahippocampal sites, but requires hippocampal involvement early on for coherent retrieval, then no mechanism is proposed by virtue of which coherent retrieval without hippocampal involvement becomes possible. Do connections that already exist become stronger? Do new connections grow among the neuronal populations involved? Is there any evidence for either of these possibilities? (but see Murre et al. 2002 for a discussion of recent attempts to address these issues).

3. The SMC, treating episodic and semantic memory as equivalent, offers no account of how, over time, episodic memories appear to become more semantic in nature. That is, we know that over time episodic detail is lost whereas "gist" is preserved, but SMC offers no way of understanding how and why this happens. The model proposed by McClelland et al. [48] does address this question, but in the process it ignores the continuing presence of episodic memory.

Given these and other weaknesses of the standard theory, Nadel and Moscovitch [61] generated a new model called the multiple trace theory (henceforth MTT; see Estes 1955 and Hintzman 1986 for mention of multiple traces in cognitive models of anterograde memory), which sought to account for the facts of systems-level consolidation in a novel way. This model built on the "cognitive map theory" of hippocampal function [64] and the component process model [49, 50] but went beyond them in a number of ways (cf. [55] for a comprehensive discussion of the relations among these models).

MTT made a range of predictions, most prominently the idea that retrieval of remote memories would engage the hippocampal complex, in contrast to what SMC predicted. In the remainder of this paper we will review the current literature, both in studies with humans and other animals, with an eye toward resolving this debate (see Moscovitch et al. [53–55] for extensive treatment of many of these issues).

We start with more precise statements of both SMC and MTT, focusing on the central predictions of each position. We then review the literature. We review studies in humans using both neuroimaging and neuropsychological methods; each approach allows one to ask different questions. We follow with a short discussion of studies in experimental

animals (mostly rodents), which have tried to unravel some of the thornier questions that often cannot be asked in studies with humans. We conclude that although some issues remain to be resolved, the weight of the evidence at present strongly favors MTT.

The two positions explained

SMC and its predictions

According to SMC, in its current incarnation, all explicit memories (e.g., both episodic and semantic) are *always* stored in extrahippocampal circuits. The hippocampal contribution is in the form of an "index," which serves to bind together the disparate neocortical sites representing the various parts of an episode, or the semantic structure abstracted from related episodes. This position seems to make a number of critical predictions that contrast it with MTT:

1. All the "information" inherent in an explicit memory is to be found in neocortical circuits, *not* in hippocampal circuits. Thus, a memory, independent of the hippocampus, contains the same information that it would contain were the hippocampal system available, either before or after the completion of consolidation (cf. p. 424 in [48]). The implication is that remote episode memories retrieved by individuals with amnesia must be as fully detailed as remote episode memories retrieved by individuals with intact brains. Note that this need not imply that remote memories contain as much detail as more recent memories, just that the absence of the hippocampus cannot influence the qualitative nature of a memory retrieved after it is consolidated (cf. p. 141 in [5]), assuming that such consolidation happened while the hippocampus was intact.
2. Given that the hippocampus is not involved in retrieval of remote memories, such retrieval should not be accompanied by activation in the hippocampus.[3]
3. Both forms of explicit memory, episodic and semantic, are treated the same with regard to systems consolidation. Both start out dependent upon the hippocampus, and both end up independent of it.

MTT and its predictions

According to MTT, memories are stored jointly in hippocampal and extrahippocampal circuits, and rather different things happen to episodic and semantic memory. This leads to a somewhat different set of predictions:

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[3] This prediction reflects the initial formulation of SMC before the advent of neuroimaging methods. Such methods make it clear that hippocampus is activated when remote memories are retrieved. Updated versions of SMC argue that such activation reflects encoding of new memories rather than retrieval of remote ones (see below).

1. The information inherent in an episodic memory is contained in both hippocampal and extrahippocampal circuits, such that remote episode memories retrieved by individuals with amnesia should *not* be qualitatively the same as remote episode memories retrieved by individuals with intact brains.

2. Given that the hippocampus *is* involved in retrieval of certain aspects of remote episode memory, such retrieval *should* be accompanied by activation in the hippocampus.

3. The two forms of explicit memory, episodic and semantic, are *not* treated the same with regard to systems consolidation. According to MTT, episodic memories always remain dependent upon hippocampal circuits, at least for their most detailed expression. Semantic memories, on the other hand, can be independent of hippocampal circuitry in just the way standard theory suggests. That is, semantic information is always represented in extrahippocampal circuits, and the process of consolidation acts to strengthen these circuits and to integrate newly acquired semantic information into existing stores.

Contrasting predictions

Given these distinctions, it is clear that three areas of empirical investigation and three seemingly simple questions are central to distinguishing between SMC and MTT:

1. Are remote memories retrieved by amnesics as fully detailed as remote memories retrieved by intact individuals (SMC) or are there qualitative differences (MTT)?

2. Is the hippocampus activated by retrieval of remote episodic memories (MTT) or not (SMC)?

3. Do episodic and semantic memories suffer the same fate during consolidation and in amnesia (SMC) or are they affected differently (MTT)?

Although these questions appear to be simple ones, of course they turn out to be much more complicated once one tries to answer them definitively. To start, the first question raises complex issues about the methods used to elicit remote memory retrievals. The second question can only be addressed in neuroimaging contexts, and runs into the problem of separating retrieval from encoding. The third question itself begs the issue of the relation between episodic and semantic memory. In the literature review that follows, we highlight these problems while trying to reach a conclusion about the merits of the two theoretical positions.

The nature of remote memory in human amnesics

Episodic memory

The initial formulation of SMC and views of systems consolidation in general had consolidation limited to weeks in rodents and monkeys and to about 3–10 years, at the outside, in humans. It is now clear, contrary to these early claims, that large MTL lesions produce a RA that extends for decades, consistent with the initial formulation of MTT, that the extent and severity of RA is determined by the size of MTL lesions (for different evidence regarding this prediction, see Kopelman et al. 2004; Gilboa et al. 2005). Having abandoned their earlier position and conceded that RA is extensive, proponents of SMC now focused their major point of contention on 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 a temporally extensive RA at all. Proponents of MTT and SMC have offered functional and anatomical accounts for the current discrepancy among studies, respectively.

According to the functional account favored by MTT, hippocampal involvement in episodic memory is defined by the recollective quality and detail of the remembered event. Because most autobiographical memories lose their vividness and detail as they age [36], memories of amnesic and normal people may *appear* equally impoverished at remote periods if memory is queried insufficiently. The Autobiographical Memory Interview (AMI) [31], a standard test of remote episodic and semantic personal memory used in most studies, may reveal differences between controls and amnesics in some cases. In other cases, however, special interviewing and scoring procedures may be needed. For example, in the patient H.M., such tests have revealed extensive memory loss dating to early life [81], although on less sensitive tests his RA appeared more limited, leading to the conclusion that his remote memories were relatively normal [11, 77].

Although Bayley et al. [5, 6], using more sensitive tests, still reported no difference between amnesic people with large MTL lesions and controls at the most remote time period, these data should be interpreted with caution. The number of details recalled by their controls was far less than that reported by controls in other studies [36], nor was there any evidence of the typical loss of memory with aging in their control subjects, a finding inconsistent with most of the work in this area. Differences in testing procedure and scoring may account for some of these discrepancies. What is more worrying, however, is this group's report that patients with lesions confined to the MTL had ungraded

deficits in semantic memory lasting at least 40 years in one study [68]. It is highly unusual for RA to be far more severe for semantic than episodic memory in such cases, suggesting that the method used by Bayley et al. to test episodic memory may not have been sensitive enough.

This point is brought out most clearly in their most recent study. Despite evidence regarding the insensitivity of the AMI, Bayley et al. (2006) used it to assess remote autobiographical memory. Not surprisingly, memory was hardly affected even for events occurring in early adulthood in people with extensive MTL damage, who also had substantial damage to the insula and inferior temporal cortex. Interestingly, however, these very same patients had an extensive RA for public (news) events, which extended to over 50 years in one case. One reason is that it was much more difficult to obtain a high score on the news events tests, which included quite difficult items (e.g., What tire manufacturer recalled thousands of tires [answer: Firestone]) compared to the test for autobiographical memory, which depended on a laxer and more subjective scoring method. Thus, whereas controls performed at or near ceiling on the AMI, receiving scores close to the maximum of 9/9, they scored at only 60% correct for recent news events, and dropped to 40% correct for news events that occurred 10 or more years earlier. These findings underscore the need to use a comparable metric for testing both types of memory, as Steinvorth et al. [81] did in their study.

The anatomical account favored by SMC 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 the neocortex, a finding supported, in part, by Bright et al. (2006). In their view, damage confined to the MTL spares memories for the most remote periods, although in the study of Bright et al, there is a suggestion that memory is impaired at the most remote period even in people with lesions confined to the hippocampus proper. The deficit fails to reach significance probably because of the low power of the test caused by variability in performance and the low number of subjects tested. Other cases, however, show RA across the life span even when the lesions are confined to the hippocampal formation (see Table 1 in [55]), and more specifically just to the fornix [67], which contains the major projections of the hippocampus. At least one of those cases, V.C., is as well documented neuroanatomically as the cases in the series of Bayley et al. [8] and, except for memory loss, is at least as cognitively intact. Moreover, the cases of Bayley et al. with the most extensive damage to MTL also have considerable damage to the insula and inferior temporal cortex, indicating that it is not likely to be the extent of extrahippocampal damage that accounts for the differences in RA observed among the different cases, but the way in which memory was evaluated.

Thus, neither the functional nor anatomical accounts seem adequate at this point because there are reports of ostensibly vivid, remote memories being spared (Bayley et al. [5, 6]) and cases with damage limited to the hippocampus proper, MTL, or its projections, who show impaired memory even at the most remote periods [8] (for more discussion, see [53–55]). For many of the same reasons, other issues are also unresolved, among them, the extent and nature of focal RA, of transient global amnesia, of the correlation between lesion size and extent of deficit ([29, 30, 32]; Gilboa et al. 2005), the unique contribution, if any, of the different regions of the MTL, and of memory loss after different types of dementia [25, 56, 59]. We believe that on balance the neuropsychological evidence concerning the status of remote memory in amnesia favors MTT, but we are aware that some of the studies are inconclusive, and others are open to different interpretations.

Some of the methodological problems associated with studying the role of the hippocampus in remote memory retrieval may be side-stepped by taking advantage of the possibility that the same brain system enabling backward mental time travel, e.g., memory retrieval, might also be critically engaged in imagining events that never happened, or that might happen in the future. This idea, brought to prominence by Tulving [86] and discussed recently by Schacter and Addis [76], has recently been tested in several studies. Ryan et al. [74] showed that the hippocampus is activated by such imaginings (see below). Given this, one wonders whether amnesic patients can imagine fictional events, either in the past or in the future. Rosenbaum et al. (2003) showed that patient K.C. was markedly impaired at imagining fictional events. Hassabis et al. [23] tested a group of amnesic patients more extensively on their ability to imagine specific future scenarios. All but one of the five patients showed profound impairment at this task.[4] What is more, the nature of the defect was quite revealing. Patients were incapable of generating a holistic representation of any imagined environment within which experiences could achieve coherence. As a consequence, they could only generate fragments that never achieved the status of an event. The authors conclude that the hippocampus "may make a critical contribution to the creation of new experiences by providing the spatial context into which the disparate elements of an experience can be bound. Given how closely imagined experiences match episodic

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[4] The patient who performed at control level had some remaining hippocampal tissue, and the authors suppose that it was this remnant that permitted imagining the future.

memories, the absence of this function mediated by the hippocampus may also fundamentally affect the ability to vividly reexperience the past." They go on to state that their findings challenge the standard theory of memory consolidation but "accord well with suggestions that the hippocampus plays a critical role in imagining experiences through the provision of spatial context, in perpetuity." It is particularly important that this study controlled for such things as salience, a sense of presence, the anterograde deficit of the patients, and any concerns one might have about the veridicality of remote memory retrievals. In so doing, this method offers a powerful approach to answering questions about the role of the hippocampus in episodic memory, and we imagine that future studies using this kind of paradigm will be important in deciding between the merits of SMC and MTT.

Semantic memory

In contrast to the controversy regarding episodic memory, there is little dispute about the fate of semantic memory. Consistent with both theories, RA for semantic information, whether for facts about oneself, about public events, personalities, or even vocabulary (see Table 1 in [55]), is either spared or confined to a period of about 10 years if the damage is limited primarily to the hippocampal formation. RA can be more extensive if the damage includes other MTL and neocortical structures, reaching the same level as autobiographical memory loss in the latter case, or possibly exceeding it in the case of patients from the series of Bayley et al. [5, 6]; Bayley et al. 2006). In a cross-sectional and longitudinal study of semantic memory for famous names and vocabulary in patients with AD, Westmacott et al. [92] 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.

Complicating the picture is the fact that semantic and episodic memories are not independent of one another. Semantic memory, for example, may benefit from episodic memory. Westmacott and Moscovitch [91] reported that episodic memory contributes to performance on tests of semantic memory. Thus, reading times and categorization by profession for famous names is faster and more accurate if the name is associated with a recollection that is of personal significance to the individual. For example, Elvis Presley may be associated with a personal visit to Graceland, whereas Frank Sinatra holds no such personal associations. Performance favors Elvis Presley, although both people are equally famous. In surveying the population, Westmacott and Moscovitch found that a common set of famous people can elicit such associations in over 80% of the population, whereas another set of equally famous people rarely elicits them. Importantly, the distinction between these two sets is absent or greatly diminished in amnesic people, and their performance on the two semantic tasks, naming and categorization, show no difference between the two sets of names.

In recent work, Moscovitch et al. (in preparation) found that in normal people, the extent to which recollection contributes to semantic memory for names and for public events diminishes with time, reaching an asymptote after 5–10 years, indicating that the facts are retained but the episodic component is absent. The temporal gradient found on tests of semantic memory in people with damage restricted to the MTL may reflect the loss of this episodic component.

Studies with animals

Because of the control over conditions during acquisition and retention, and over the location and size of lesions, studies of nonhuman mammals may help resolve some of the problems encountered in the human literature. Over the years a number of paradigms have been developed to study RA, primarily in rodents, and have yielded the same three patterns of RA after lesions to the hippocampus and related MTL structures in humans: RA with a temporal gradient, extensive RA with no gradient, and no RA. For example, several studies on contextual fear conditioning (e.g., [28]) and socially acquired taste preferences (e.g., [93]) have reported temporally graded RA in rats with hippocampal lesions. By contrast, in studies of remote spatial memory, the typical finding is temporally extensive RA either without a gradient (e.g., [58]), or with poorest memory for the most remote time periods [94]. Finally, no RA is reported on tasks in which there is no anterograde loss after hippocampal lesions, such as procedural learning, single object discrimination, or conditioning to unimodal stimuli, such as tones.

In reviewing the evidence, Rosenbaum et al. [71] accounted for much of it by positing that tests dependent on relational context (e.g., allocentric and configural spatial cues) produced a temporally extensive RA, whereas tests that are less dependent on relational context (tone, taste, or smell of conditioning stimulus) produced either a temporally graded RA or no RA. Recent studies have confirmed this hypothesis. Thus, memory for a hidden platform in a water maze (e.g., [9, 45, 82] or for the rewarded side in a cross maze [94, 95], both open to a complex environment, was impaired after hippocampal lesions even if acquisition was months earlier. RA was not influenced by lesion size. On the other hand, memory for particular objects either showed a temporal gradient or no memory loss at all after hippocampal lesions [58], but a temporally extensive RA after perirhinal lesions in both rats [17, 57] and monkeys [84].

If we consider memories dependent on relational context to be analogous to episodic memory in humans, and the other two types of memory to be analogous to familiarity or semantic memory, then the general pattern of results resembles that found in humans with hippocampal lesions. This line of reasoning suggests a new interpretation of the temporal gradient observed in certain tasks such as contextual fear conditioning and acquired food preference. Rather than view the temporal gradient as evidence in favor of SMC, we can interpret it as evidence of transformation of memory representations over time from ones that are context-dependent shortly after acquisition, and rely on the hippocampus, to ones that are less dependent on context afterward, and, thus, exist independently of the hippocampus. Consistent with the latter interpretation, a number of investigators have shown that sensitivity to contextual detail diminishes with time, such that animals generalize conditioned behaviors to novel contexts as the retention interval increases. This result has been obtained both in the conditioned fear paradigm ([4, 39, 47]; Houston et al. 1999; Wiltgen and Silva, submitted for publication; Winocur and Moscovitch, submitted for publication) and in a socially acquired food preference task (Winocur and Moscovitch, submitted for publication). Similar transformations can occur with respect to complex spatial memories. With time and experience spatial memories are also transformed from contextually dependent ones to more schematic ones that can be sustained by extrahippocampal structures. In line with this interpretation, Winocur et al. [94, 95] found that rats reared in a complex environment learned the rewarded locations in that environment, and retained those memories even after hippocampal lesions. The same rats, however, were impaired in acquiring new spatial memories in a different environment. These results are consistent with reports of the effects of hippocampal lesions on remote spatial memory in humans, who can also navigate normally in an environment learned long before they sustained their damage. Although they base their navigation on a schematic, map-like representation of the environment, they do not retain details, which prevents them from recreating the original environment and reexperiencing it in rich detail. The absence of a detailed representation may also prevent rodents and humans from navigating their environment with optimum efficiency. Thus, even those rats with hippocampal lesions who navigated the complex spatial maze with relatively few errors chose less efficient routes to rewarded locations than did intact animals (Winocur and Moscovitch, in preparation).

The transformation hypothesis also helps explain some intriguing results based on the so-called reconsolidation paradigm. Once reactivated, a memory trace that was presumably consolidated and no longer dependent on the hippocampus becomes labile and susceptible to hippocampal lesions shortly after it has been reactivated [34]. In other words, once retrieved, a memory trace needs to be reconsolidated or consolidated anew. We would suggest that reconsolidation is a demonstration of the dynamic nature of memory, always capable of being transformed depending on the availability of cues. Reexposing the rat to the initial training environment reactivates the original, context-dependent memory representation that relies on the hippocampus, and memory for the task once again becomes susceptible to hippocampal lesions. As already noted, sensitivity to context in contextual fear conditioning is diminished with time, in keeping with its increasing independence of the hippocampus. However, providing a reminder restores that sensitivity (Winocur et al., in preparation).

Hippocampal activation during retrieval of remote memory?

Episodic memory

Most neuroimaging studies of autobiographical (episodic) memory report equivalent activation in the MTL to retrieval of recent and remote episodic memory, especially in the hippocampus, as predicted by MTT and contrary to SMC. This pattern of activation is obtained in PET and fMRI regardless of the interval, which varies from days [69, 80] to weeks ([37], in parahippocampal cortex) to decades [75] or the particular procedures used to elicit and test autobiographical memories: recognition of sentences describing events [40, 41, 43, 69] and reexperiencing events in response to cue words [1, 2, 10, 21, 75], generic sentences [69], and family photos [18]. Both hippocampi are typically activated in comparison to a variety of baseline tasks. Even in a person with hippocampal lesions who was amnesic from early childhood, activation of residual hippocampal tissue was found for the very few remote episodic memories he had [43].

One criticism leveled against such neuroimaging studies is that hippocampal activation might be associated with the encoding of memories retrieved in the scanner, rather than with retrieval of the memories themselves. A number of controls suggest this is not the case. First, hippocampal activations are not obtained for semantic or generic memories retrieved in the scanner, which would presumably also be encoded [40, 41, 43, 69, 87]. 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 [18]. This finding was recently replicated in a study comparing real and imagined events ([74]; Cox et al., in preparation), even though the

imagined events were highly detailed and contained the same components as real autobiographical experiences (e.g., including familiar people, places, and objects within the imagined event). What is most interesting is that in the study of Gilboa et al. [18], although there was equivalent activation for vivid recent and remote memories, the activations were distributed differently. Activations associated with recent memories clustered at the anterior end of the hippocampus, whereas those associated with remote memories were distributed throughout its length. These results using imagined events as the baseline condition are particularly striking in view of the recent finding, discussed earlier, that the hippocampus is probably critical to such imaginings [23]. This baseline condition must have activated the hippocampus, and the fact that remote memory retrievals activated the hippocampus to a greater extent shows that such retrievals constitute a very powerful activator of hippocampal circuits.

A few studies show a temporal gradient of activation [16, 66], but in these studies there was either no control for vividness, number of details or personal significance [85], 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. [15] note that older memories are typically sketchier and more semantic than recent ones and Addis et al. [1] have shown that hippocampal activation is modulated by vividness, emotionality, and personal significance: memories rated high on those qualities in the scanner led to greater hippocampal activation. Although memory recency 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 (see also [21]). The only exception with regard to recency is a study by Maguire and Frith [41] who found a temporal gradient of activation in the right hippocampus in older, but not younger, adults. The cause of this anomaly is not apparent (see [18] for possible interpretation). Overall, these studies provide strong support for predictions based on MTT. Although hippocampal activation is moderated by variables that may be related to the age of the memory, it is important to note that no studies to date have shown a complete lack of hippocampal activation for very remote events, as SMC would predict.

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, and those have found either no hippocampal activation; hippocampal activation without a gradient for personal semantics, knowledge of public events, [40] and famous faces [7, 27, 35]; or a temporally graded activation in right entorhinal cortex to famous faces [22] and in right parahippocampal cortex to names [12]. In all cases, the time range sampled was greater than 20 years, extending as high as 50 years [22]. The source of the discrepancy is difficult to determine at present (see [55] for discussion).

The temporal gradient observed in some studies of semantic memory is consistent with MTT and SMC in that they both suggest that hippocampal involvement in retention and retrieval of semantic memory diminishes with time. Other studies, reporting the absence of a temporal gradient favor MTT to the extent that such gradients reflect the contribution of an episodic component.

In addition to these studies of semantic memory, there are a handful of functional neuroimaging studies on remote spatial memory. Maguire et al. [42] 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 wayfinding, but the region of activation is in the parahippocampal cortex, not in the hippocampus itself. Likewise, in a test that required participants to reexperience an event in a particular location (combined spatial and autobiographical memory test), Niki and Luo [63] found greater activation in the left parahippocampal gyrus when contrasting recent (within 2 years) detailed events with remote (7 years) detailed events. In a complex study contrasting different types of spatial, semantic, and episodic memory acquired recently (within weeks at most) or 4 years earlier, Mayes et al. [46] report 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. The hippocampal activation might be related to the spatial nature of the memory, or to the vividness (number of details of the environment and autobiographical context) of the experience, much as was found for hippocampal activation of episodic memory (see above). In both of the studies, however, there was also activation in precuneus, parietal, parahippocampal, and posterior cingulate cortex, structures that appear to be part of a spatial network [72].

Medial temporal regions may be particularly involved in recollection of the spatial component of a memory, although the particular site of activation may differ depending upon the specific requirements of the task. Hayes et al. [24] had subjects view a videotaped tour of four houses, and then compared activation for three aspects of episodic memory; memory for objects, temporal order, and spatial location of objects. Whereas activation in the hippocampus

proper was similar across the three conditions, bilateral parahippocampal cortex activation was greater for spatial location compared to object and temporal order information. Several recent studies in our laboratory (Ryan et al., in preparation; Hoscheidt et al., in preparation) suggest that this difference is observed regardless of whether the source of the to-be-recalled information is episodic or semantic; tasks that emphasize spatial location or spatial relations show greater activation in parahippocampal cortex, hippocampus proper, or both. However, the activation within the hippocampus proper during semantic retrieval occurs in the anterior third of the hippocampus, whereas activation associated with episodic retrieval is clearly posterior, often extending into adjacent parahippocampal cortex.

Rosenbaum et al. [72] used a version of the Toronto Public Places Test, modified for scanning. They found that the hippocampus proper was not activated on any of the tests more than on the baseline control task, although the parahippocampal cortex was active, as noted by Maguire et al. The level of activation in extrahippocampal 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 [20]. The only evidence of hippocampal activation to familiar places comes from studies in which there is some personal, spatial reasoning [19, 33, 63], suggesting that the experiential component might be crucial.

Neuroimaging evidence on remote spatial memory is consistent with both MTT and SMC, which claim, for different reasons, that remote spatial memories can exist independently of the hippocampus. As we suggested elsewhere [53–55, 70, 94, 95], it is possible that remote spatial memories existing independently of the hippocampus are coarser than those dependent on the hippocampus.

Conclusion

The literature provides relatively clear answers to the questions we raised at the outset to distinguish the SMC and MTT:

1. Are the remote memories retrieved by people with MTL amnesia as fully detailed as the remote memories retrieved by intact individuals?

When the most sensitive methods are used to assess remembered detail, the data show that remote memories retrieved by amnesic patients are detail-poor compared to the remote memories retrieved by appropriate control subjects.

In both the spatial and nonspatial domains, remote memories retrieved by amnesic patients lack rich contextual detail.

2. Is the hippocampal complex activated by retrieval of remote episode memories?

The hippocampal complex is most definitely activated during the retrieval of remote episodic memory. This does not appear to reflect mere reencoding that might occur when an old memory is brought back to conscious awareness.

3. Do episodic and semantic memories suffer the same fate during consolidation and in amnesia?

Most definitely not. In accordance with MTT, but not with SMC, episodic and semantic memories fare quite differently over the course of consolidation.

We submit that the empirical data are not consistent with SMC. They are, however, consistent with many of the assertions of MTT. However, there are aspects of MTT, at least as first formulated, that are not so well supported. We initially argued that the extent of the gradient in RA should vary as a function of the size of the hippocampal complex lesion [61]. This prediction was related to the notion that each time an episodic memory is retrieved a "replicate" trace is created within the hippocampal complex, spreading out the representation of that memory. This spread would mean that larger lesions are required to knock out older memories, on average.

However, the evidence in support of these particular predictions is inconsistent ([32], but see Gilboa et al. 2005), suggesting that the specific mechanism we proposed to account for the continuing hippocampal involvement in episodic memory over time might have been incorrect. The evidence strongly supports this continuing involvement, however, so we should consider other mechanisms that would accomplish this function.

Trace replication is but a specific example of the more general idea that when an episode memory is reinstated, its representation within hippocampal circuits is altered. Other forms of alteration are possible, such as strengthening the existing trace, or changing it by incorporating some new information as represented in additional neuronal circuits. In most circumstances this alteration will lead both to an incorporation of new information into the memory trace, and a concomitant strengthening of the trace as a result of the reconsolidation process itself. Further discussion of this possibility is beyond the scope of the present review, but we imagine that development of this idea and the linkages between MTT and reconsolidation will be well worth pursuing in the future.

The evidence reviewed in this paper provides a unified framework for conceptualizing hippocampal–neocortical interactions [53, 54, 71]. In this framework, *detailed*

representations of remote events (episodic, autobiographical memory in humans and context-dependent memory in animals), including *rich spatial representations* of environments, are hippocampally 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.

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 ([13, 14, 26, 52, 96], but see Wais et al. 2006). 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 and scripted. What is more, retrieval appears to reinstantiate a previously stored and consolidated memory, which can then be transformed by the subsequent retrieval context.

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