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Memory formation and long-term retention in humans and animals: Convergence towards a transformation account of hippocampal–neocortical interactions

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ABSTRACT

Historically, the hippocampus has been viewed as a temporary memory structure. Consistent with the central premise of standard consolidation theory (SCT), a memory is initially hippocampus-dependent but, over time, it undergoes a consolidation process and eventually becoming represented in a distributed cortical network independent of the hippocampus. In this paper, we review evidence that is incompatible with each of the following essential features of SCT that are derived from its central premise: (1) Hippocampal damage reliably produces temporally graded retrograde amnesia, (2) all declarative explicit memories are equivalent with respect to consolidation, (3) consolidation entails a process of duplication in which a particular cortically based memory is identical to the hippocampus-dependent memory from which it derived, (4) consolidated memories are permanent and immutable. We propose an alternative hypothesis that assumes a transformation process and changes in the memory over time. Building on multiple trace theory (Nadel & Moscovitch, 1997), the transformation hypothesis contains three key elements that differentiate it from SCT: (1) An initially formed memory, which is assumed to be episodic and context-bound, remains dependent on the hippocampus *for as long as it is available*, (2) with time and experience, a hippocampal memory supports the development, in neocortex, of a less integrated, *schematic version*, which retains the gist of the original memory, but few of its contextual details, (3) there is a *dynamic interplay* between the two types of memory such that one or another may be dominant, depending on the circumstances at retrieval. Evidence is provided in support of the transformation hypothesis, which is advanced as a framework for unifying the seemingly disparate results of studies of anterograde and retrograde memory in the animal and human literatures.

Since the classic work of Brenda Milner and her colleagues (Penfield & Milner, 1958; Scoville & Milner, 1957), we have known that bilateral lesions to the medial temporal lobes (MTL), that include the hippocampus, produce a profound anterograde amnesia that is characterized by impaired long-term memory in the face of preserved intelligence, perception and short-term memory. In addition, such patients exhibit a temporally graded retrograde amnesia (RA) in which information acquired shortly before surgery is lost whereas older memories are retained. Historically, this pattern of lost and spared memory has been interpreted in terms of standard consolidation theory (SCT) originally formulated in the 19th century (Burnham, 1904; Muller & Pilzecker, 1900; Ribot, 1882). The central feature of SCT is the idea that the formation of durable long-term memories, from transient short-term memories, is a time-dependent process (Hebb, 1949). Initially, retention and retrieval of long-term memories rely on the hippocampus, but eventually become independent of it as the memories become consolidated in extra-hippocampal (presumably neocortical) structures. Evidence consistent with SCT has also been reported in studies of animals subjected to hippocampal ablation and other amnestic treatments (Agranoff & Davis, 1967; Duncan, 1949; Winocur, 1985). Although not always explicitly stated, it is impor-

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tant to emphasize that, by this view, consolidated memories retain the same features as when they were represented initially in the hippocampus.

SCT, which views the consolidation process as a unitary process that proceeds linearly to final completion, was formulated at a time when memory itself was conceived by most people as a unitary construct. Over the years, the theory has undergone modifications in light of new developments in memory research. For example, as new findings pointed to the existence of multiple memory systems, evidence from numerous sources indicated that the MTL, and the hippocampus in particular, is implicated only in a specific type of memory. There is much debate as to how hippocampus-dependent memory is best characterized but there is consensus that the hippocampus is necessary for acquisition, retention and retrieval of (explicit or declarative) memories that deal with conscious recollection of facts and episodes. Other non-declarative forms of memory, such as those related to motor and perceptual learning, priming, and the acquisition of habits, skills and rules, do not require the hippocampus and are unaffected by lesions or other forms of disruption. Taking this into account, the scope of SCT is now restricted to explicit or declarative memory.

At the outset, it should be noted that neurobiological research has distinguished between two general types of consolidation: (1) a rapid initial process that entails cellular and synaptic reorganization that is believed to occur over short periods of time following training (seconds to hours, depending on the task) and to implicate all types of memory in all organisms, and (2) a second, more prolonged process related to changes in distributed neural systems that can extend over periods of time ranging from several days to many months, even years. Because changes in the representation of a long-term memory trace occur across different brain regions, this process is referred to as *systems-level consolidation* (Dudai, 2004). The great variation in the presumed time-course of systems-level consolidation undoubtedly depends on several factors, most importantly species and task. At our current level of understanding, we make the simplifying assumption that essential consolidation processes are comparable across these time courses.

In recent years, experimental findings have appeared in both the human and animal literatures that appear to be in conflict with SCT. This is especially the case with respect to the severity and extent of RA following MTL damage or inactivation (Clark, Broadbent, & Squire, 2005a; Clark, Broadbent, & Squire, 2005b; Rudy & Sutherland, 2008; Winocur, Moscovitch, Caruana, & Binns, 2005; Winocur, Moscovitch, Fogel, Rosenbaum, & Sekeres, 2005), and the role of the hippocampus in remote memory (Fuji, Moscovitch, & Nadel, 2000; Viskontas, McAndrews, & Moscovitch, 2000). Reinforced by evidence from neuroimaging studies, these inconsistencies led investigators to question some of SCT's essential features, and to formulate different views of the consolidation process as well as the nature of hippocampal involvement in that process. In this paper, we show how animal models inform and complement research on humans to help resolve some of these inconsistencies.

1. A critique of SCT and a new approach

We focus on areas of research that have yielded results that are incompatible with four essential features of SCT: (1) temporally graded RA; (2) the equivalence of episodic and semantic memory with respect to consolidation processes; (3) the duplication of the hippocampus-dependent memory in neocortex during consolidation and (4) the immutability (permanence) of the consolidated memory. We deal with each of these issues in turn, and, in the process, show how they are inter-related. Based on this critique, and the evidence we report, we advance a new framework that resolves apparent contradictions in the literature and captures the relationships between the hippocampus and other structures that are involved in memory formation and representation.

In contrast to SCT which assumes linearity between the initially formed memory and the consolidated version, we assume a transformation process which entails a change in the characteristics of the memory with time. We take issue with the idea that systems-level consolidation entails merely the establishment of a duplicate, but now permanent, version of the hippocampus-dependent memory. Following other theoretical positions, such as multiple trace theory (MTT—see below), our framework has three key elements: (1) The initially formed memory, which we assume to be episodic and contextually bound, remains dependent on the hippocampus for as long as it retains episodic features. (2) Over time and experience, this memory supports the development in neocortex of a schematic version of the original memory which retains some of its essential features and meaning, but few of its contextual details. (3) There is a dynamic interplay between the two types of memory such that one or the other may be dominant depending on their relative strength and the circumstances that elicit them at retrieval. As a result, retention and retrieval are continually evolving processes in which the memories can interact and influence each other.

The first two points are derived from Nadel and Moscovitch's formulation of MTT (Nadel & Moscovitch, 1997; Nadel & Moscovitch, 1998). Briefly, according to MTT, when an event is experienced and represented as an episodic memory, the trace consists of an ensemble of bound hippocampal and neocortical neurons. Each time a memory is retrieved, it is re-encoded automatically by the hippocampus along with the context in which the retrieval occurred. The older the episodic memory, the more traces there are of that memory, and the more opportunity there is for its retrieval. Based on statistical regularity across memories, neocortical structures extract what is common across the various contexts and derive the gist of the event independent of context. Similar processes mediated by neocortex are involved in abstracting semantic information from episodic memory. Thus, the hippocampus is always necessary for representing detailed, episodic memories of an event. As well, it plays a facilitatory role in forming, in neocortical structures, a schematic version of that memory that embodies the gist of the event as well as related semantic information (see McClelland, McNaughton, & O'Reilly, 1994 for a computational model on the interaction of hippocampus and neocortex in incorporating information from episodic to semantic memory). The third point develops implications inherent in the first two points and together with them constitutes the foundation of the transformation hypothesis which informs this paper.

1.1. Retrograde amnesia is not always temporally graded

It was evident from the outset that temporally graded RA is a characteristic feature of the amnesic syndrome in patients of various etiologies. With respect to MTL amnesia, this pattern was first observed in the classic bitemporal patient, HM, by Milner and her collaborators, and formally investigated by Marslen-Wilson and Teuber (1975). In the latter study, HM, a group of head-injured patients with primarily frontal-lobe damage, and healthy controls were required to recognize faces of people who became famous at different times over a 50-year period (see Fig. 1). Healthy controls and head-injured patients showed the standard forgetting curve in which recently formed memories were remembered better than older memories. In contrast, HM showed very poor memory for people who became famous after his injury, or for several years preceding it, but normal memory for people who were famous before then.

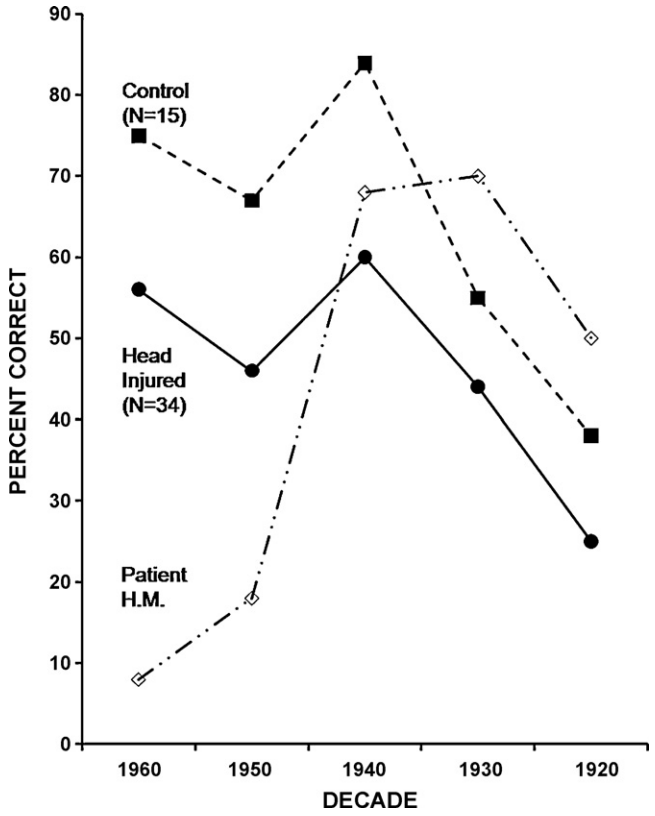

Fig. 1. Temporally graded retrograde amnesia in the medial temporal lobe patient, HM.
From Marslen-Wilson and Teuber (1975).

According to SCT, recent memories are vulnerable to effects of hippocampal damage because the consolidation process is not yet complete. Since the memory is still represented in the hippocampus, damage to the hippocampus would eliminate the memory. At longer delays, after consolidation has run its course, the memory becomes established in neocortical structures and, therefore, would be unaffected by hippocampal lesions.

Although the conclusions drawn from this study were meant to apply to all declarative or explicit memories, it must be noted that identifying well known personalities, such as Franklin Roosevelt, is primarily a test of semantic memory, that is memory for knowledge and general information. In this sense, semantic memory must be distinguished from episodic memory of an event that is tied to the temporal–spatial context associated with its acquisition. This distinction between semantic and episodic memory, forcefully articulated by Tulving (1972), is crucial to the point of view we are advancing, as will become increasingly apparent throughout the paper.

The episodic-semantic distinction becomes important in the RA literature when one appreciates that temporally graded RA is not consistently observed in patients with MTL amnesia. A survey of studies of remote memory in patients with MTL amnesia since HM shows that there are at least as many reports of memory loss with no temporal gradient as there are with a gradient (see Table 1). Indeed, in some cases, not only was there no gradient, but severe memory loss was observed virtually across the entire lifespan. Even when a gradient was reported, the extent of RA often spanned decades, leaving only the very earliest memories intact (see Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006). Interestingly, in several of the studies, the very same patients with MTL amnesia exhibited both patterns, amnesia with and without a temporal gradient. A review of the studies listed in Table 1 suggests that, for the most part, ungraded memory loss in MTL patients is associated with tests of episodic memory that assess, for example, recall of personalized autobiographical experiences, whereas graded effects were observed primarily when semantic memory was assessed. A notable exception to this pattern is found in studies of episodic memory by Squire and his colleagues who consistently report temporally graded RA in patients with hippocampal damage (Kirwan, Bayley, Galvan, & Squire, 2008; Reed & Squire, 1998; Rempel-Clower, Zola-Morgan, Squire, & Amaral, 1996), although other investigators, working with comparable patients and the same tests did not find this effect (e.g., Rosenbaum et al., 2008). It is also noteworthy, with respect to semantic memory, that several studies reported non-graded amnesia in similar patients on tests of famous faces and public events (e.g., Cipolotti et al., 2001; Sanders & Warrington, 1971 [updated in Warrington & Duchen, 1992]; Warrington & McCarthy, 1988), which might be viewed as measures of factual or semantic memory. In fact, the particular tests used in these studies assess memory for personalities who, for the most part, were famous for a brief time and then disappeared from the public stage (Warrington's Famous Faces Test), or ask very specific questions about events that may require precise knowledge related to one's personal experience (Public Events Questionnaire). To the extent that these tests tap into episodic memory, they disadvantage hippocampally damaged individuals.

Before 1990, animal studies of RA in relation to consolidation processes typically involved non-specific treatments such as electroconvulsive shock or systemic protein-synthesis inhibitors, and relatively short retention intervals of seconds to hours. Such pro-

Table 1
Retrograde amnesia in humans with hippocampal damage.

Temporal gradient	No gradient
Scoville and Milner (1957)	Sanders and Warrington (1971)
Marslen-Wilson and Teuber (1975)	Cermak and O'Connor (1983)
Cermak and O'Connor (1983)	Damasio, Eslinger, Damasio, Van Hoesen, and Cornell (1985)
Corkin (1984)	Tulving, Schacter, McLachlan, and Moscovitch (1988)
Barr, Goldberg, Wasserstein, and Novelly (1990)	Warrington and McCarthy (1988)
O'Connor, Butters, Miliotis, Eslinger, and Cermak, 1992	Barr et al. (1990)
Rempel-Clower et al. (1996)	Victor (1990)
Reed and Squire (1998)	O'Connor et al. (1992)
Kapur and Brooks (1999)	Kartsounis, Rudge, and Stevens (1995)
Kopelman, Stanhope, and Kingsley (1999)	Hirano and Noguchi (1998)
Bayley, Hopkins, and Squire (2003)	Kopelman et al. (1999)
Bayley, Hopkins, and Squire (2006)	Viskontas et al. (2000)
Wais et al. (2006)	Cipolotti et al. (2001)
Kirwan et al. (2008)	Steinvorth et al. (2005)
	Bright et al., 2006
	Chan, Henley, Rossor, and Warrington (2007)
	Noulhiane et al. (2007)

Table 2
Retrograde amnesia in animals with hippocampal damage.

Temporal gradient	No gradient
Winocur (1990)	Salmon, Zola-Morgan, and Squire (1985)
Zola-Morgan and Squire (1990)	Gaffan (1993)
Kim and Fanselow (1992)	Bolhuis, Stewart, and Forrest (1994)
Vnek and Rothblat (1993)	Broadbent et al. (2006)
Kim, Clark, and Thompson (1995)	Cho, Kesner, and Brodale (1995)
Maren, Aharonov, and Fanselow (1997)	Anagnostaras, Gale, and Fanselow (2001)
Anagnostaras et al. (1999)	Koerner, Thomas, Weisend, & Sutherland (1996)
Winocur, McDonald, and Moscovitch (2001)	Weisend, Astur, and Sutherland (1996)
Clark, Broadbent, Zola, and Squire (2002)	Mumby, Astur, Weisend, and Sutherland (1999)
Takehara, Kawahara, and Kirino (2003)	Sutherland et al. (2001)
Ross and Eichenbaum (2006)	Gaskin, Tremblay, and Mumby (2003)
Tse et al. (2007)	Clark et al. (2005a,b)
Gaskin, Tardif, and Mumby (2009)	Driscoll, Howard, Prusky, Rudy, and Sutherland (2005)
Ramos (2009)	Martin, de Hoz, and Morris (2005)
Quinn, Ma, Tinsley, Koch, and Fanselow (2008)	Winocur et al. (2005a, 2005b)
	Wiltgen, Sanders, Anagnostaras, Sage, and Fanselow (2006)
	Broadbent et al. (2006)
	Lehmann et al. (2007)
	Epp et al. (2008)
	Haijima and Ichitani (2008)
	Sutherland, O'Brien, and Lehmann (2008)

cesses likely implicated synaptic-level consolidation. After 1990, with the advent of sensitive behavioural tests, investigators began to study systems-level consolidation by examining the effects of hippocampal lesions at much longer intervals, spanning days to months. In one of the first such studies, Winocur (1990) adapted Galef's (Galef & Wigmore, 1983) socially acquired food preference test to track the time it takes memory to become independent of the hippocampus. In this test, a subject-rat (***S***) is paired with a demonstrator-rat (***D***) that has just sampled a food with a distinctive odour. At a later time, when tested in the same context, and given a choice between that food and an unfamiliar one, *S* shows a distinct preference for the food associated with the familiar odour. Rats with hippocampal lesions were found to acquire the food preference as well as normal rats but they forgot it at an accelerated rate, indicating anterograde amnesia. In tests of remote memory, hippocampal lesions eliminated memory for the acquired preference when the delay between acquisition and surgery was short, on the order of a day or two, but not at longer delays. This finding of temporally graded RA paralleled the results of human studies with HM and other MTL amnesics, and was interpreted as consistent with SCT. The same pattern was observed in other studies involving different tasks and different species (Kim & Fanselow, 1992; Zola-Morgan & Squire, 1990).

As researchers continued to investigate the effects of hippocampal lesions on remote memory in animals, contradictory findings emerged. For example, Sutherland et al. (2001) trained rats preoperatively to find a hidden platform in the Morris water maze, and lesioned the hippocampus 2 weeks or 14 weeks after acquisition. The results showed extensive RA at both delays with no evidence of a gradient. Other studies demonstrated ungraded RA in rats with hippocampal lesions over longer acquisition-surgery delays (e.g., Clark et al., 2005a, 2005b), even extending as far back as 9 months (Winocur, Moscovitch, Caruana, et al., 2005). A review of animal studies of RA following hippocampal lesions conducted to date reveals, as in human studies, that ungraded RA is reported at least as often as graded RA (see Table 2).

While there are some unexplained inconsistencies in Table 2, such as the same type of task yielding different effects (e.g., contextual fear conditioning, discrimination learning) which we will discuss later, the important finding, as in human studies, is that there is not an invariable pattern of temporally graded RA following hippocampal lesions. On some tests, damage to the hippocampus leads to a severe and temporally extensive RA without a gradient. These findings are all the more compelling since, unlike human studies, the location and extent of lesion are relatively well-controlled.

1.1.1. Summary

There is converging evidence in the animal and human literatures that temporally graded RA is not an invariant result of hippocampal lesions. For some memories there is extensive, ungraded RA, whereas for others there is a graded pattern. Extra-hippocampal damage cannot account for this pattern which undermines one of the crucial tenets of SCT. Instead, the type of memory that is tested seems to be a crucial factor.

1.2. Are all remote declarative, explicit memories affected equally by hippocampal lesions?

A review of inconsistencies in the human and animal literatures suggests that the different gradients in RA are dependent on the type of memory that is tested, as well as on affected structures. In humans, following on Kinsbourne and Woods' initial observation that amnesia affects episodic, but not semantic memory (Kinsbourne & Wood, 1975), we note above that when lesions affect the MTL, and the hippocampus in particular, temporal gradients are observed primarily on semantic memory tasks, such as identifying or recognizing public events or figures, or words that entered the language at different points in one's lifetime, whereas non-graded or very extensive amnesia is associated with tests of episodic memory, such as describing autobiographical episodes. It is important to note, however, that some tests have both episodic and semantic components, such as recounting a vacation in Paris where one can draw on general knowledge about the city and also report events that are unique to the individual's vacation. As we discuss below, techniques have been devised to tease apart the semantic and episodic components of an event, and when they are applied, only the latter shows an extensive RA without a gradient following MTL damage. However, as the lesion extends beyond the MTL, the semantic component also shows an extensive RA (Fujii et al., 2000; Manns, Hopkins, & Squire, 2003; Poreh et al., 2006; Squire & Bayley, 2007; Viskontas et al., 2000).

Neuroimaging studies have provided important evidence that the hippocampus is implicated in remote memory for autobiographical episodes no matter when they occurred. Using a variety of

techniques from verification of sentences describing events related by the participants themselves to relating event-details based on family photographs supplied by confederates, investigators noted that the hippocampus is activated equally regardless of the age of the retrieved memories (Piolino, Desgranges, & Eustache, 2009). A crucial determinant in this work was the vividness of the recalled event, which is an index of its episodic quality. Because recent memories are likely to be recalled in more detail than remote ones, hippocampal activation may sometimes show a temporal gradient if vividness, and other indices of the episodic aspect of the memory, are not taken into account. When the effect of vividness is controlled either experimentally or statistically, variation of hippocampal activation with age is eliminated.

By comparison, studies examining remote memory for semantic material, such as faces or names of famous people, or public events, have yielded more variable results. Some investigators have reported a temporal gradient with greater hippocampal activation for recent than remote events (Moscovitch, 2008; Moscovitch et al., 2006; Nadel, Winocur, Ryan, & Moscovitch, 2007), whereas others find a pattern that resembles episodic memory, with equivalent hippocampal activation across the lifespan (Piolino et al., 2004). The reason for the discrepancy is not apparent, but one possibility, as indicated earlier, is that some public events and personalities also evoke an episodic memory, and insofar as they do, then hippocampal activation will also be found for remote events. Recent studies that support this interpretation will be discussed in the section that considers the co-existence of episodic and semantic information.

Clearly, the episodic-semantic distinction, which incorporates autobiographical memory and language, is not applicable in all respects to the study of memory in animals, but important parallels can be drawn. In a previous paper, we suggested that contextually dependent memories in animals were analogous to episodic memory in humans (Rosenbaum, Winocur, & Moscovitch, 2001). The argument is that both entail representations that incorporate the rich spatial–temporal context in which they were acquired, and both are equally dependent on the hippocampus. Typically, in animals, contextually dependent memories refer to learning relationships among co-occurring elements in a particular environment, as in contextual fear conditioning, or in conventional tests of spatial learning and memory (e.g., Morris water maze). We also proposed that, in animals, non-contextual memories are analogous to semantic or non-declarative memory in humans. Thus, memory for particular objects, responses, or stimulus-response associations, can be recovered without reference to the context in which they had been experienced, but depend, instead, on isolated features which elicit particular responses (see also Eichenbaum, Yonelinas, & Ranganath, 2007 on the distinction between relational and non-relational memory).

How best to characterize contextual and non-contextual memories has been hotly debated in the literature without a resolution being reached, Indeed, some authors have argued cogently that the crucial distinction in memory is as much between different kinds of context, as between contextual and non-contextual memories (Nadel & Wilner, 1980; Rudy, 2009). Although there is no universal agreement about what qualifies as a hippocampus-dependent context and what does not, the following is a first-order approximation that captures a consistent theme in the animal literature. Contextual memories are those that are configural, detailed and well-integrated, thereby affording flexibility in manipulating the memory representation and in guiding responses, while retaining great specificity. By contrast, the other type of memory, which we will call schematic, is a less detailed collection of cues and features which are not integrated with one another, and consequently cannot be manipulated flexibly. In our conceptualization, contextual and schematic memories correspond generally to episodic and semantic memories, respectively, in humans.

The distinction between contextual and non-contextual memories is reflected as well in tests of RA in animal models, paralleling those in humans on episodic and semantic memory (see above). There is extensive RA without a temporal gradient for tests that are context-dependent. Many of these are conventional tests of spatial memory (Clark et al., 2005a, 2005b; Sutherland et al., 2001; Winocur, Moscovitch, Caruana, et al., 2005), the presumption being that on those tests a specific location must be remembered in relation to a specific context defined by the configuration of environmental cues. By comparison, a temporal gradient is observed on most tests of memory that are not context-specific suggesting that the hippocampus contributes initially to their formation but ultimately relinquishes its involvement once consolidation is complete (Tse et al., 2007; Winocur, 1990; Zola-Morgan & Squire, 1990). In addition, there are tests, such as contextual fear conditioning, which appear to be context-specific, yet show a temporal gradient. Our research, which we describe below, shows that in such cases, the gradient reflects changes in the nature of the representation of the memory from a context-dependent to a context-independent memory consistent with the transformation framework.

1.2.1. Summary

The evidence suggests that memories mediated by the hippocampus are fundamentally different from those which are mediated by extra-hippocampal structures. An important implication of these observations is that the hippocampus is concerned primarily with episodic memory, the conscious recollection of detailed, autobiographical events in humans or the storage and recovery of contextually specific memories in animals. When the hippocampus is damaged, such memories are impaired regardless of their age. The hippocampus also contributes to the formation of semantic or non-contextual, schematic memories which are then represented in neocortical structures, independently of the hippocampus. Damage to the hippocampus shortly after an event will produce amnesia for that event if the semantic or schematic version of the memory has not yet formed. However, if the semantic/schematic memory is available, it can be used in many cases, thereby accounting for the temporal gradient associated with MTL lesions.

1.3. Is the memory that becomes represented in neocortex the same as the initial memory in the hippocampus?

A central premise of SCT is that the memory that becomes established with time in neocortex is the same memory that was initially represented in the hippocampus. How then does SCT account for the different gradients observed in animals and patients with hippocampal lesions on tests of remote memory? There appear to be two answers: (1) The presence or absence of a gradient, particularly in humans, depends on lesion size and location. That is, lesions confined to the hippocampus always are accompanied by a temporal gradient, and its absence is the result of the lesion extending to extra-hippocampal structures. (2) If successful performance of the memory task requires on-line hippocampal processing, in addition to retrieval of the remote memory, then no temporal gradient is expected.

The latter argument must be considered speculative as there have been no studies to our knowledge that have directly tested this hypothesis. The evidence in favour of the first argument is offset by a substantial literature that runs counter to it. For example, as noted earlier, the observation that sometimes, the very same amnesic patients show both types of memory loss argues strongly against a structural interpretation of the discrepancy (see Table 1). The human literature highlights the importance of distinguishing between episodic and semantic memory, and using tests that are differentially sensitive to each type. When these conditions are met, numerous examples can be found of patients with lesions to the

hippocampal system who have extensive RA for episodic memory regardless of the extent of extra-hippocampal damage. In some cases, the lesions are extremely localized, e.g. to the fornix, and yet the patients still show a RA for episodic memory that extends over the entire lifetime. With respect to semantic memory, however, the very same patients have preserved memory, or at worst an amnesia that is restricted to the decade preceding the injury (for reviews favouring both sides of the debate, see Moscovitch et al., 2005; Rosenbaum et al., 2008; Shrager, Kirwan, & Squire, 2008; Squire & Bayley, 2007). There is a similar duality in the animal literature. As already noted, some tests, particularly those involving spatial memory, yield RA without a gradient, whereas other tests, such as socially acquired food preference and contextual fear conditioning, yield a temporally graded RA (but see Epp et al., 2008; Lehmann, Lacanilao, & Sutherland, 2007; Sutherland et al., 2001; Sutherland, O'Brien, & Lehmann, 2008).

Our alternative view is that memories that are 'consolidated' in neocortex are fundamentally different from those that were initially dependent on the hippocampus. We propose that in the intact brain, memory is *transformed* from one that is initially context-dependent and represented in the hippocampus to one that is context-independent and represented in neocortical structures outside the hippocampus. This does not imply, however, that the context-independent memory always replaces the context-dependent, hippocampal memory. Although some hippocampal memories may be lost over time, in other cases, as we shall see in human and animal studies, both memories may continue to be available. We review the evidence that supports these proposals below.

We focus first on the animal literature because here one can follow the development of a memory over long periods of time relative to the lifespan of the animal, whereas such prospective studies are impractical in humans (but see study by Hirshhorn below). As indicated above, two commonly used tasks in the study of RA in rats are socially acquired food preference and contextual fear conditioning, both of which yield temporally graded memory loss. Interpreting these results in the framework of SCT, the assumption is that the memory is the same at both ends of the spectrum. This critical assumption, however, has never been tested. According to the transformation hypothesis, the memory that is retrieved shortly after acquisition and is dependent on the hippocampus has different characteristics from the one that is retrieved later and is no longer hippocampus-dependent. In other words, the former should be context-dependent whereas the latter should be less so.

We tested these alternative interpretations in both the food-preference and contextual fear conditioning tasks (Winocur, Moscovitch, & Sekeres, 2007). We chose these tasks not only because they are commonly used in studying remote memory, but also because we wanted to establish some general principles across tests that differ in the type of information processed, in response characteristics, the nature of reinforcement, and in the time course to establish a permanent memory. In this study, normal rats and rats with hippocampal lesions were trained on the food-preference or contextual fear conditioning task following our standard procedures. Their memories were then tested, at short or long delays, in either the same training environment (CXT-A) or a novel environment (CXT-B). The results were the same for both the food-preference (Fig. 2A) and contextual fear conditioning tasks (Fig. 2B). At short delays, normal rats' memory was context-specific in that they exhibited the learned responses to a much greater degree in CXT-A than in CXT-B. At long delays the normal rats no longer discriminated between the original and novel environments and, indeed, there was no difference in the strength of the recalled responses in the two environments. The hippocampal groups were unresponsive to differences in the test environments and, in the respective tasks, exhibited the same patterns of performance when tested in CXT-A or CXT-B.

The context-specificity of a recently acquired contextual fear memory was confirmed recently in normal mice by Wiltgen and Silva (2007), who also systematically examined changes in context specificity with the passage of time. These authors showed that, on this task, normal mice discriminated equally well between training and novel environments for up to 14 days following fear conditioning. At longer delays, in line with the transformation hypothesis, discrimination began to break down and, by 36 days, the mice were freezing equally in both environments (see also Wang et al., 2007). These observations are consistent with the interpretation of an expanded generalization gradient over time, caused by forgetting-induced degradation of the initial memory (Riccio, Ackil, & Burch-Vernon, 1992). By our view, it is important to distinguish between a continuum of degradation across all attributes of a memory from those that define only the contextual features of a memory whose loss reflects the declining role of the hippocampus.[1]

From these studies we conclude that when memories are initially formed they are closely linked to a specific context and, as such, can be considered episodic in nature. With time, a transformation process occurs in which a schematic memory forms that is less rigidly tied to the specific context in which it was acquired. If the hippocampus is removed or rendered dysfunctional before the transformation process is complete, then memory loss ensues because the only memory that is viable is the context-specific memory represented in the hippocampus. Hence, the poor memory exhibited by MTL amnesics and animals with hippocampal lesions for events experienced shortly before the damage in tests of remote memory. If hippocampal function is disrupted after the transformation process is complete, the context-specific memory is lost but the semantic or schematic memory can be used to retrieve the learned response. This explains the sparing of memories in instances of temporally graded RA in animals and humans with hippocampal damage.

As we noted earlier, the initial context-specific memory may have decayed or may continue to be available in the intact brain, along with the schematic memory, even after transformation has occurred. As we will show in the next section, an appropriate reminder can reinstate some context-specific memories. In the remainder of this section, we review evidence from different types of human studies that semantic memories derive from episodic memories, and that the two types of memory can co-exist in ways that are consistent with the transformation hypotheses.

Nelson (1974) and Markman (1989) report evidence that, when children acquire words and the concepts they denote, they do so in relation to specific experiences. Thus, for example, the word 'dog' initially is linked to the episode or context in which it was first uttered. It is only with multiple repetitions and experiences with dogs across different contexts that the word's full meaning is abstracted, to include only those aspects which are common across episodes. In this way, the notion of 'dog' becomes conceptualized and takes on meaning that is independent of any particular context.

[1] It should also be emphasized that, while context-specific memories may be susceptible to decay over time, the formation of non-hippocampal, context-general or schematic memories is not necessarily dependent on that process, though in some cases there may be a relationship between them (Wiltgen & Silva, 2007). It is possible to extend the context-specific effect, for example, by increasing exposure to the conditioning environment before training (Biedenkapp & Rudy, 2007), or by providing a reminder experience after training (Winocur et al., 2009). However, both of these manipulations could be interpreted either as having prevented or reversed the decay of the context-specific memory or, as we have argued, increased the dominance of that memory, relative to the context-general memory (see pp. 26–28 below and Winocur et al., 2009).

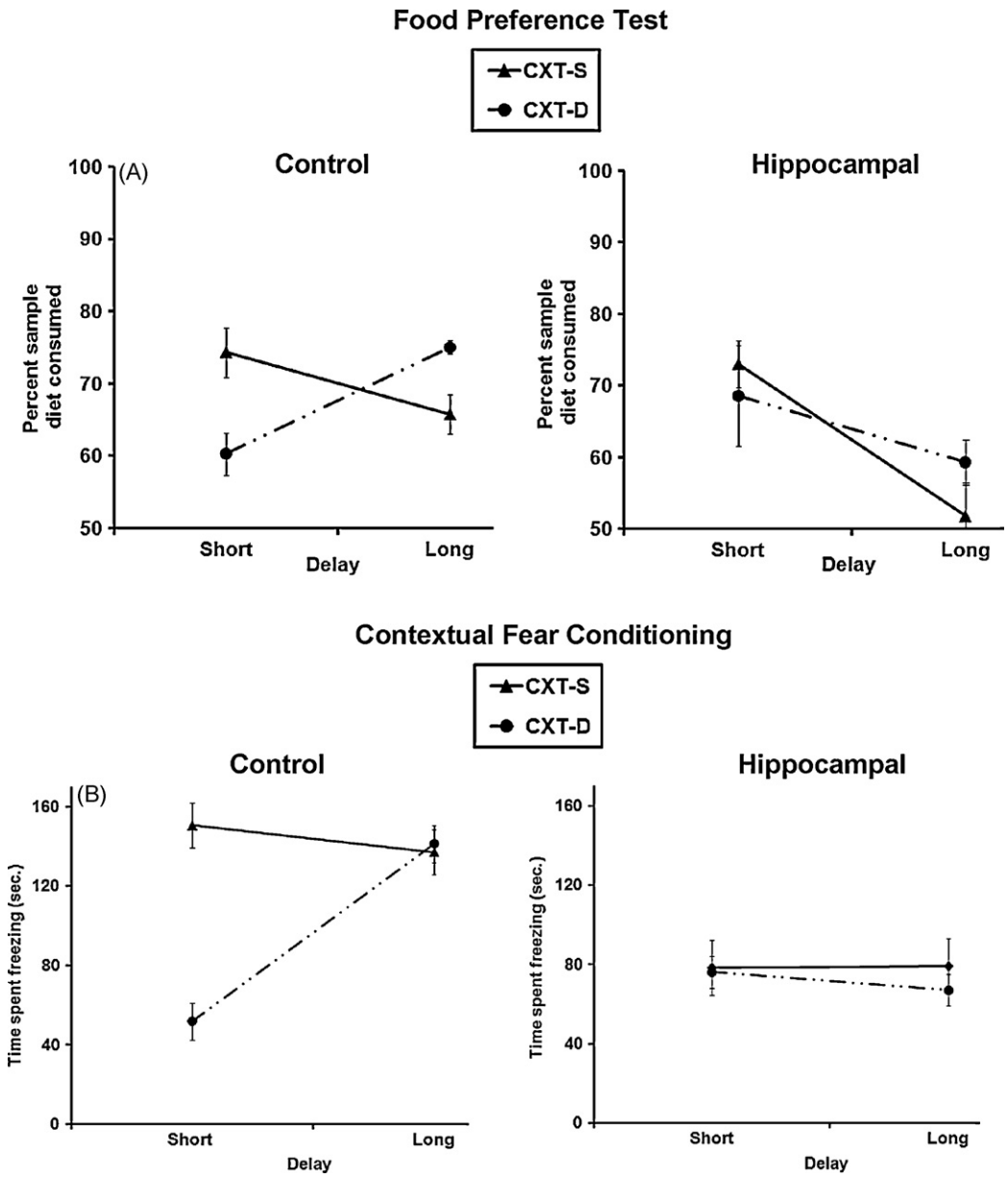

Fig. 2. Effects of context manipulation on performance in the food preference test (A) and contextual fear conditioning (B). On both tasks, control rats exhibited context-specificity at short, but not long, delays. Hippocampal groups did not respond to context manipulations in either task. (CXT-S denotes that rats were trained and tested in the same context; CXT-D denotes that rats were trained and tested in different environments).
From Winocur et al. (2007).

In an excellent review paper on episodic and semantic aspects of autobiographical memory, Conway (2009) notes that similar processes can operate in adulthood. In the vast majority of cases, the perceptual details that characterize episodic memories and allow accurate re-experiencing of the past, are lost within days of the event. What remains are schematic memories that retain the gist of what occurred. Eventually even the gist component may pass leaving only a semantic residue which is incorporated into a more general autobiographical schema or a semantic memory system. Such a 'forgetting' process may complement the process of abstraction of word meaning from the different contexts in which they were encountered.

In some cases, memories can retain their episodic aspects, coexist with semantic memories, and even interact with the gist that was gleaned from the semantic memories. This was shown by Westmacott and Moscovitch (2003) who had participants rate names of famous people along semantic dimensions such as familiarity, frequency, and general facts known about each person, as well as along episodic dimensions, such as how personally significant the names were to them and whether they conjure an episode (recollection) associated with that name. They found that names that were rated highly on recollection were recalled and recognized better, led to faster fame judgement, and were even read more quickly than names that were low on recollection, even though both types were equated in terms of semantic information (see also Westmacott, Black, Freedman, & Moscovitch, 2004).

As has been noted frequently (e.g., Conway, 2009; Levine, Svoboda, Hay, & Winocur, 2002; Moscovitch, 2008; Piolino et al., 2009), autobiographical memories often consist of episodic and semantic information. To disentangle one type of information from the other, recently developed tests allow for the separation of episodic and semantic memories in autobiographic memory. Levine et al. (2002) devised a test with a scoring system that credits the number of details contained in a narrative about a particular

episode. The details are classified as *internal* if they are peculiar to the episode, and can be construed as reflecting episodic memories; and *external* if they are generic or tangential to the episode, and can be construed more as semantic [See Piolino, Desgranges, Benali, and Eustache (2002) for another test that combines elements of the approaches taken by Levine et al. (2002), and Westmacott and Moscovitch (2003).].

The various instruments have been used in several behavioural and functional neuroimaging studies involving different populations, including patients with focal lesions, those in early stages of dementia, and normal old adults. With few exceptions, the results of these studies are consistent with evidence from the animal literature, and favour the transformation hypothesis over SCT. Damage to the MTL, particularly to the hippocampus and related structures in the extended hippocampal system, was associated with loss of episodic components of memory for events and personalities. By comparison, there was little effect on the semantic components of memories for the same events and people. Instead, loss of semantic aspects of memory was associated with the extent of damage to neocortical structures such as the anterior and lateral temporal lobes, particularly on the left side.

The effect of the memory's age on loss of the episodic component in patients with hippocampal damage has also been investigated. Once again, in line with the transformation hypothesis, the majority of studies found that loss of the episodic component was unrelated to age of the memory, with losses dating back to early childhood, and with no evidence of a temporal gradient. Thus, for example, Westmacott, Freedman, Black, Stokes, and Moscovitch (2004) found that the processing advantage conferred by high recollection names, relative to low recollection famous names, is lost in people with MTL lesions no matter how long ago the names became famous, though processing of the semantic component was unaffected. Likewise, Steinvorth, Levine, and Corkin (2005) reported a loss of internal details for memories covering the entire lifespan both in patients with focal MTL lesions, including HM, and in patients with MTL degeneration. By comparison, there was considerable sparing of external details. See Piolino et al. (2009) for similar findings. Evidence that this selective loss of the episodic component is not the result of brain damage in general comes from studies of patients in the early stages of semantic dementia whose damage affects primarily neocortical structures concerned with semantics, such as the anterior and lateral temporal cortex, but not medial temporal structures. Such patients show relative sparing of the episodic component with loss of semantics (Maguire, Kumaran, Hassabis, & Kopelam, 2010; Moss, Kopelman, Cappalletti, De Mornay Davies, & Jaldow, 2003).

Further, studies of patients with Alzheimer's disease provide important evidence against the argument that the absence of a temporal gradient in episodic memory is associated only with lesions extending beyond the hippocampus to include lateral temporal cortex. For example, Gilboa et al. (2005) showed that the extent of extra-hippocampal damage was not a contributing factor to the loss of episodic memory. Instead, as noted above, damage to anterior and lateral temporal neocortex led to selective loss of semantic memory. As dementia of the Alzheimer's type progresses, semantic memory loss is more temporally extensive, as gauged by patients' inability to recognize names as famous and to identify the meaning of words which entered the public lexicon over the last 50 years (Westmacott, Freedman, et al., 2004). These findings suggest that the degree of neocortical degeneration which marks the progression of the disease after its initial stages, determines the extent of temporally graded RA for semantic memory.

The same pattern of hippocampal and neocortical contribution to episodic and semantic components of autobiographical memories are found in functional neuroimaging studies of healthy controls. The extent of hippocampal activation is determined by the episodic aspects of the memory of the event and not by its age. To be sure, some studies have shown a temporal gradient of hippocampal activation with age, but that is only because older memories typically have less of an episodic component than recent memories (Niki & Luo, 2002; Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003). When episodic qualities such as vividness, personal significance, and recollection are controlled, the effect of age on hippocampal activation is eliminated (Addis, Moscovitch, Crawley, & McAndrews, 2004; Gilboa et al., 2006; Piolino et al., 2009). The effects of episodic component on neocortical activation are more variable, but in general, neocortical activation is associated with semantic components.

All models of memory consolidation, including the transformation hypothesis, posit that the hippocampus helps support the development of the representation of semantic memory in neocortex. Consistent with these models, individuals with MTL lesions often exhibit a temporally graded RA for semantic information related to vocabulary, public events and personalities, as well as personal knowledge (see reviews by Fujii et al., 2000; Moscovitch et al., 2005; Squire & Bayley, 2007). The RA in these cases is on the order of a decade, suggesting that during that interval some of the information is still linked to an episodic component and derived from it. Results from studies using functional neuroimaging, though variable, generally support this conclusion. Activation of the hippocampus and related MTL structures is diminished with time while neocortical activation increases or remains the same (see review by Piolino et al. (2009), as well as Viskontas, Carr, Engel, and Knowlton (2009), Wais, Wixted, Hopkins, and Squire (2006), for similar results).

Although the hippocampus contributes to and facilitates the acquisition of semantic memory and its neocortical representation in normal individuals, studies have shown that adult amnesic patients with hippocampal damage can acquire semantic memories, though the process is laboriously slow and the knowledge gained in terms of amount and depth is low (Manns et al., 2003; O'Kane, Kensinger, & Corkin, 2004; Verfaellie, Koseff, & Alexander, 2000; Westmacott & Moscovitch, 2001). Studies of people who sustained hippocampal damage in childhood, however, show that by adulthood, they have good semantic knowledge, suggesting that perhaps regions of neocortex implicated in semantic memory representation are more plastic in childhood than adulthood, or perhaps that different strategies were used to acquire this knowledge (Squire & Zola, 1998; Vargha-Khadem et al., 1997) which may not be hippocampally dependent (Bauer, 2008; Bloom & Markson, 1998; Carey & Bartlett, 1978).

1.3.1. Summary

Contrary to the notion that the 'consolidated' neocortical memory is a duplicate of the pre-consolidated hippocampal memory, we provide evidence that the two memories have different characteristics. We propose a transformation process that converts the initial, context-specific hippocampal memory to a non-contextual schematic memory that is represented extra-hippocampally. Whereas the former type of memory is lost following hippocampal damage, the latter is preserved, thereby accounting for the temporal gradients observed in retrograde amnesia. We also note that both types of memory can be available concurrently and, consistent with the transformation hypothesis, one or the other memory is impaired disproportionately, depending on whether the hippocampus or neocortex is damaged.

1.4. Are long-term (consolidated) memories immutable?

According to SCT, when memories are consolidated in extra-hippocampal structures, they are fixed and highly resistant to disruption. The considerable evidence from animal and human

studies showing that long-term memories are unaffected by a variety of amnestic agents (e.g., ECS, lesions, hypoxia) is consistent with this view. However, a serious challenge to this essential feature of SCT emerged from studies in the 1960s, which utilized a 'reminder' paradigm. The typical procedure was to train animals on various tasks (e.g., avoidance conditioning, maze learning) and, after a period of time that presumably was long enough for the consolidation process to be complete, re-expose them to the learning environment without reinforcement. When an amnestic agent was administered shortly after the reminder experience, the effect was to eliminate memory of the learned response. In his review of this literature, Lewis (1979) noted that this treatment-induced memory loss is contrary to the predictions of consolidation theory. Interestingly, as an alternative, he argued that short- and long-term memories exist in different 'states', each with its own unique characteristics. According to Lewis (1979), memories in the short-term state are vulnerable to disruption, while memories in the long-term state are not.

In recent years, the work of Sara (1973), Nader, Schafe, and Le Doux (2000), and others (e.g., Debiec, LeDoux, & Nader, 2002; Eisenberg & Dudai, 2004; Milekic & Alberini, 2002), using different tasks and more exacting methods, replicated the early findings and sparked renewed interest in reactivated memories, particularly as they relate to consolidation processes. One influential view is that the effect of a reminder on stable, long-term memories is to restore them to a labile state during which they once again become dependent on the hippocampus and related structures, as in the early stages of consolidation. The reactivated memories then undergo a process of *reconsolidation* until they are re-established in neocortical structures. Until that process is complete they are once again susceptible to the types of treatment that interfere with hippocampal function (Nader & Hardt, 2009).

There has been considerable debate as to whether consolidation and reconsolidation processes are identical because, while there are similarities in terms of molecular mechanisms and implicated brain regions, there are also important differences (Dudai, 2006; Nader & Hardt, 2009). As well, investigators have offered different explanations of the nature and formation of reminder-induced memories (Alberini, 2005). Notwithstanding differences in interpreting reactivated memories and uncertainties over their functional significance, the reminder effect has been demonstrated reliably and clearly runs counter to the immutability principle of SCT. To account for reconsolidation, SCT would have to assume the transfer or relocation of the consolidated memory from neocortex back to hippocampus.

The transformation hypothesis offers a different perspective on reminder-induced reactivated memories. According to this view, prior to the reminder, the schematic or context-general version of the target memory likely prevails. The effect of reminding the animal in the training environment is to restore the dominance of the context-specific memory. Thus, when tested shortly after the reminder experience, normal rats should once again discriminate between the original environment and a novel environment. Hippocampal lesions, produced between the reminder and the test, would be expected to eliminate the context-specific memory. It also follows that, if rats were reminded in a novel environment that shared at least some cues with the original environment, the schematic memory would be evoked. Following such a reminder, normal and hippocampus-lesioned rats should exhibit memory for the learned response when tested in either environment.

These predictions were confirmed in a recent study in which normal rats acquired a contextual fear response in a particular environment (CXT A) and, after a 28-day delay, were reminded in the same or a different (CXT B) environment before undergoing hippocampal surgery (Winocur, Frankland, Sekeres, Fogel, & Moscovitch, 2009). As can be seen in Fig. 3, the memory that was re-activated by CXT-A was context-specific and eliminated by hippocampal lesions.[2] This finding parallels that of Debiec et al. (2002) who reported that memory for a reactivated hippocampus-based contextual fear response was disrupted similarly by intra-hippocampal infusions of the protein synthesis inhibitor, anisomycin. In contrast, the memory reactivated by CXT-B was schematic and unaffected by hippocampal lesions (see also Wiltgen & Silva, 2007). These results, which relate to the loss of reactivated memory following hippocampal disruption to changes in memory representation, further underscore the dynamic interplay between the two memories. Just as a memory undergoes qualitative changes from context-specific to schematic as the memory becomes represented in extra-hippocampal structures during the consolidation/transformation process, these results show that a reverse-like process occurs during reconsolidation. That is, following a reminder in the original training environment, the dominance of a context-general memory can be over-ridden by the re-emergence of the context-specific memory. In an interesting complement to these observations, Biedenkapp and Rudy (2007) showed that exposure to the learning context (CXT A) prior to training can also maintain the context specificity of the acquired memory at long delays. It remains to be seen whether a context-specific memory protected in this way is as susceptible to amnestic agents as one reactivated by a reminder.

There is little research involving humans on reconsolidation. In one interesting study (Sackeim et al., 2000), patients scheduled for electroconvulsive treatment learned a list of paired-words and, later, were reminded of the learning experience prior to receiving treatment. When tested after treatment, memory loss for previously studied words was greater in those patients that received the reminder than those that did not. In a different approach, Brunet et al. (2008) used pharmacological interventions that were similar to those that were effective in preventing reconsolidation of fear-based learning in rats. Working with people diagnosed with post-traumatic stress disorder, these investigators showed that a reminder of a traumatic event, followed by administration of the β-adrenergic blocker, propranolol, led to diminished emotional responsiveness to the traumatic memory if treatment was delivered soon after the reactivation experience (see Forcato et al. (2007), and Hupbach, Gomez, Hardt, and Nadel (2007), for demonstrations of the reactivation effect in humans in purely behavioural studies).

1.4.1. Summary

The results of studies involving the reactivation or reconsolidation paradigm question the assumption of SCT that consolidated memories are immutable. Consistent with the transformation hypothesis, we show that reminders operate by reactivating

[2] Interestingly, the lesion also eliminated expression of the context-general memory under these conditions. While this outcome was not necessarily predicted by the transformation hypothesis, a possible explanation is that, over the 24-h period between the reminder and surgery during which the context-specific, hippocampus-dependent memory became dominant once again, neocortically mediated context-general memories were inhibited or 'overshadowed' (Anagnostaras, Maren, & Fanselow, 1999; Eisenberg & Dudai, 2004; Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998). This inhibitory process may be considered analogous to the supremacy of hippocampal memories vis-à-vis memories mediated by other neural systems (e.g., Packard & McGaugh, 1992; Sutherland, Lehmann, Spanswick, Sparks, & Melvin, 2006). In considering the mechanism of such an inhibitory effect, one possibility is that the specific reminder of the hippocampal memory (i.e., re-exposure to CXT-A) initiates a retrieval process which, once enacted, blocks access to the general memory for a period of time, even if the specific memory is no longer available. Although the inhibitory or retrieval effects outlast the removal of the hippocampus, it is entirely possible that they are not permanent, and that the context-general memory may recover with time.

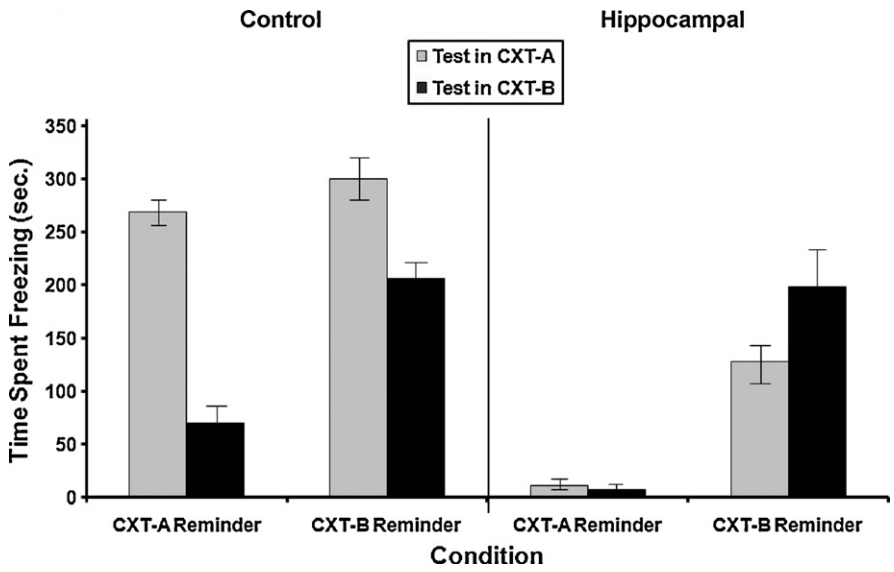

Fig. 3. Following the reconsolidation paradigm, in a test of contextual fear conditioning, reminding the rat in the original conditioning environment (CXT-A) reactivated the hippocampus-based, context-specific memory and rendered it vulnerable to the effects of hippocampal lesions. When the rat was reminded in a different environment (CXT-B), the context-general or schematic memory was reactivated and hippocampal lesions had no effect.
From Winocur et al. (2009).

context-specific or schematic memories. Insofar as the memories are context-specific, they continue to be dependent on the hippocampus and once again can be disrupted by damage to that structure. When schematic memories are elicited, they are represented in neocortex, and are unaffected by hippocampal damage. By this view, the ends of the continuum that define systems-level consolidation and reconsolidation, are not memories that are labile or permanent, but rather memories that exist in two different forms, context-specific and schematic, and are represented in different structures. The two types of memory can co-exist and assume dominance depending, in part, on retrieval cues (reminders).

1.5. The special case of spatial memory

Since the publication of O'Keefe and Nadel's (1978) classic volume, "The Hippocampus as a Cognitive Map", considerable attention has focused on the role of the hippocampus in spatial memory. O'Keefe and Nadel distinguished between allocentric spatial memory which depends on forming relationships among distal environmental cues, and other forms, such as memory for particular landmarks, routes, and egocentrically based representations, which do not depend on configural relationships. Evidence from studies using a diverse range of methodologies has consistently implicated the hippocampus in learning and remembering spatial locations based on allocentric, configural cues, but not on other types of spatial memory. For ease of presentation, we will refer to allocentric spatial memory simply as spatial memory, unless specified otherwise.

Despite the great interest in spatial memory, there has been very little research into the representation of remote spatial memories. Extrapolating from the tenets of cognitive map theory, there is no distinction at the neural level between spatial memories acquired recently or long ago. The hippocampus is necessary for representing allocentric spatial memories whenever they were formed.

This position stands in marked contrast to SCT which does not distinguish between spatial and non-spatial memories as far as representation in the brain is concerned. According to SCT, for both types of memory, the hippocampus plays a time-limited role in the early stages of memory formation after which they are represented in neocortical structures. It follows then that premorbid spatial memories should be affected in the same way by hippocampal damage—that is, they should be lost if acquired shortly before the lesion but spared if they are old enough to have become consolidated. Moreover, as with other types of memories, consolidated and pre-consolidated spatial memories differ only with respect to their permanence and locus of representation, and not with the nature of the information that is represented.

The transformation hypothesis combines elements of SCT and cognitive map theory, yet is distinct from both. Like cognitive map theory, the transformation hypothesis maintains that the hippocampus is implicated as long as the spatial memory is dependent on contextual cues, and that damage to the structure would disrupt the memory regardless of when it was formed. The term 'contextual' encompasses the allocentric spatial representations of cognitive map theory, but also includes environmental details such as aspects of landmarks and sensory features that are integrated with allocentric cues, and in combination with them, distinguish one environment from another. Like SCT, the transformation hypothesis posits that spatial memory can change its neural representation over time and with experience, so that a memory that once was dependent on the hippocampus can now be represented by extra-hippocampal structures alone. Unlike SCT, however, the transformation hypothesis predicts that extensive and varied interaction with the environment leads to the formation of a spatial memory that is fundamentally different from the initial memory. The detailed, contextual spatial memory is transformed to a schematic map outside the hippocampus. In this regard, spatial memories, in principle, are similar to representations of non-spatial remote memories that typically are spared following hippocampal damage. This type of memory retains allocentric spatial information that could support reasonably accurate spatial navigation following hippocampal lesions in rats, as in humans, but with differences that are commensurate with differences in the respective memories.

Although there has been little, systematic investigation of remote spatial memory, the available evidence from studies of humans and rodents favours the transformation hypothesis. We briefly review the evidence from studies in humans before turning to rodents.

Contrary to cognitive map theory, but in line with SCT and the transformation hypothesis, the available evidence indicates considerable sparing of remote spatial memories in humans with hippocampal damage. Early, mainly anecdotal observations of spatial memory in HM and other MTL amnesics, indicated that such patients could navigate normally in environments with which they had considerable pre-morbid experience (Beatty, Bierley, & Boyd, 1985; Milner, Corkin, & Teuber, 1968; Zola-Morgan, Squire, & Amaral, 1986). More recently, systematic investigations were conducted on two well documented amnesic patients with large bilateral hippocampal lesions (Rosenbaum et al., 2000; Teng & Squire, 1999). Despite being incapable of new spatial learning, they exhibited excellent spatial memory of old neighbourhoods in which they had lived for some time before their injury. For example, Rosenbaum et al.'s patient, KC, exhibited normal spatial memory of his neighbourhood on a variety of tests including, placing locations in the proper sequence along a route, distance estimation, proximity judgments, finding the shortest route to a location when the main route is blocked, and vector mapping which consists of drawing a vector in the correct direction and of appropriate length from a depicted location to another, unseen location. The results of the latter two tests are considered prototypical, cognitive map tests because they indicate that the individual has an integrated representation of locations and the relations among them. It appears that the amnesic patients' prior experience with their neighbourhoods, while undoubtedly resulting in hippocampally dependent cognitive maps of the environment, also allowed for the abstraction of general features of that map and the formation of an extra-hippocampal representation that could support navigation within the environment.

It is significant, however, that KC's preserved spatial memory was deficient in some respects, suggesting, contrary to SCT, that it was represented differently from pre-consolidated memory. He was impaired at recognizing perceptual details of landmarks, such as very familiar houses, as evidenced by his inability to distinguish photos of these houses from similar ones that belonged in another, unfamiliar neighbourhood. As well, when facing a particular landmark, he was unable to imagine what was directly behind him. Such a pattern of preserved and impaired aspects of spatial memory is consistent with the transformation hypothesis in that extra-hippocampal representations are seen as schematic, retaining sufficient skeletal information about locations and their relations to enable navigation, but lacking in perceptual detail and a full appreciation of the relation of non-salient landmarks to each other. In other words, the role the hippocampus in spatial navigation appears to be comparable to its role in memory for autobiographical episodes and semantic information.

It is instructive in this regard to consider the case of a highly experienced London taxi driver who sustained hippocampal lesions after an attack of herpes simplex virus. Maguire and her colleagues tested his navigational abilities on a display of London through which he could navigate a virtual taxi (Maguire, Nannery, & Spiers, 2006). He was slightly impaired at identifying landmarks, but nonetheless could navigate normally on London's main thoroughfares (A-routes). On the other hand, he was markedly impaired in navigating through London's side streets (B-routes) which require a much higher level of fine discrimination and greater attention to detail than do the main thoroughfares. It is this representation of detail, evident as much in spatial memory as in non-spatial autobiographical memory, that requires the hippocampus no matter how long ago the memory was acquired.

Studies of other patients suggest that the components of the schematic spatial representation are distributed across a network of extra-hippocampal structures. Those structures include the parahippocampal cortex, the posterior cingulate and retrosplenial cortex, and the parietal cortex. Damage to these structures is likely to cause much more severe deficits in navigation than damage to the hippocampus, the type of deficits being related to the function of the structure that was damaged (Aguirre, Zarahn, & D'Esposito, 1998; Epstein, Higgins, Jablonski, & Feiler, 2007; Rosenbaum, Gao, Richards, Black, & Moscovitch, 2005).

These conclusions are supported by functional neuroimaging studies of remote spatial memory. Using fMRI and the mental navigation tasks that were administered to their brain-damaged patients, Rosenbaum, Winocur, Grady, Ziegler, and Moscovitch (2007) found that the pattern of brain activation in normal adults in a highly familiar environment was consistent with predictions derived from the patient studies. That is, there was no hippocampal activation on any of the navigation tasks, though significant activation was observed in the network of extra-hippocampal structures that lesion studies from other laboratories had identified as crucial. Maguire, Woollett, and Spiers (2006) reported comparable results in their neuroimaging studies of healthy taxi drivers during mental navigation through London on virtual displays. Sometimes, the hippocampus was activated when the instructions were to get from one place to another, as if the hippocampus were involved in planning the route, but on other occasions navigation proceeded normally without hippocampal activation.

In a recently completed study that tracked the development of spatial memory for a large scale environment, Hirshhorn et al. (in preparation) administered, in a scanner, Rosenbaum, et al.'s (2005) spatial tasks to healthy young adults at two time points: first, within 6 months of their arrival to Toronto when they were just becoming familiar with the city, and then a year later when they were much more familiar with it. As predicted by the transformation hypothesis (and SCT), initially the hippocampus was activated during performance of those tasks that were considered allocentric. A year later, hippocampal activation was lost, and replaced by activation in the same extra-hippocampal regions reported by Rosenbaum et al. (2005) in people who had lived in Toronto for many years.

Studies of remote spatial memory in rodents have yielded results remarkably similar to those in humans if the animal is given sufficient time to acquaint itself with the environment prior to hippocampal lesions, but not when exposure to the complex environment is relatively brief. Most commonly used tests of spatial memory in rats (e.g., Morris water maze, cross-maze) are of the latter type. That is, animals are trained to learn a fixed location following a limited number of trials administered from a limited perspective. For purposes of processing spatial information, this may be inadequate to enable the formation of a schematic cortical map that could accurately guide place finding in the absence of the hippocampus. In such cases, hippocampal lesions consistently produce an ungraded amnesia that extends over the length of the test period and for as long as 9 months before surgery (Clark et al., 2005a, 2005b; Sutherland et al., 2001; Winocur, Moscovitch, Caruana, et al., 2005; see Ramos, 1998, for one of the few exceptions to this common finding).

Winocur, Moscovitch, Fogel, et al. (2005) noted the critical difference in the way human and animal studies of spatial memory are conducted and asked if rats with hippocampal lesions, like comparably damaged humans, would show preserved spatial memory if they were given the opportunity to become familiar with the environment before surgery. To answer this question, groups of rats were reared socially in a specially designed complex environment ('village') with different rewards (e.g., food, water) always available in fixed locations. After 3 months, hippocampal or sham surgery was performed and, after recovery, the rats' memory for specific reward locations was tested in the same environment. As in studies with humans, the results showed clearly that there was no difference in the ability of hippocampal and control groups to find the reward compartments. By comparison, rats with hippocampal

lesions that had no prior experience in the village were severely impaired in learning the locations of the rewards.

A series of probe trials showed that the village-reared hippocampal groups, like the control groups, used allocentric spatial strategies to navigate the village, rather than egocentric strategies, or stimulus-response strategies based on local or sensory cues. When familiar cues could be used to guide behaviour accurately, rats with hippocampal lesions performed as well as controls and, interestingly, this was also the case when only a few of the original cues were present. The latter results suggest that they relied on a configuration of cues, so that only a subset of them was required for correct performance. However, when it was necessary to find the goal compartment on the basis of a new set of spatial relationships, as when the village was moved to a different room, or rotated in relation to the external environment in the same room, hippocampally lesioned rats were severely impaired.

Further evidence about the nature of the extra-hippocampal memory, and how it differs from hippocampal memories, comes from recent follow-up work on rats that had become familiar with the village environment before the lesion (Winocur, Moscovitch, Rosenbaum, & Sekeres, 2010). In that study, rats were tested post-operatively in the same environment but, on half the trials, barriers were placed along preferred routes to the goal compartments. As in our previous work, rats with hippocampal lesions continued to use a spatial strategy, but as a result of encountering barriers, they took longer than controls to regroup and find the compartment. These results show that hippocampally lesioned animals are not as flexible in their use of spatial cues even when the relation between all distal cues and locations within the village are held constant.[3]

These findings reinforce the human studies in showing that, with sufficient exposure to the environment, spatial memories can survive hippocampal damage. However, as indicated by the worse performance of hippocampally lesioned rats on some of the probe tests, these memories, represented as they are in extra-hippocampal structures, are not the same as those mediated by the hippocampus in the intact brain. Interestingly, a similar conclusion was reached by Wang, Teixeira, Wheeler, and Frankland (2009) who found that mice with hippocampal lesions retained a pre-operatively learned, context-dependent, discrimination response, when the lesion was made at a long delay following training. However, although their spared memory contained contextual associations, further testing revealed that this memory was more fragile and vulnerable to extinction than that expressed by controls. Like the village studies, their experiment suggests that, under certain conditions, some context specificity can be supported by extra-hippocampal structures but that the representation of a remote memory in a hippocampally lesioned brain is not equivalent to that in an intact brain.

The rats' behaviour in our spatial-navigation tasks provide clues about the nature of the schematic representations, and how they differ from spatial representations in the intact brain. To account for aspects of allocentric spatial memory that are preserved, we argue that these extra-hippocampal, schematic representations are comprised of a distribution of neural ensembles that represent discrete elements of the distal environment which can provide spatial references for guiding navigation. These neural elements, however, are not integrated with each other. By contrast, representations of spatial memory that involve the hippocampus consist of a rich network of linkages among the elements that permit efficient learning and flexible responses to spatial challenges, such as performing efficiently on the blocked routes. With respect to humans, such integration may be necessary for retaining many non-essential, perceptual details and for preserving knowledge about minor routes and their relation to each other and to major ones (see Rudy, 2009, for a similar characterization related to contextual fear conditioning).

Our village studies provide evidence that, in terms of memory formation and long-term representation, spatial memories undergo a process that is similar to that of non-spatial memories. That process represents a transformation from a context-specific memory that is part of a detailed and coherent cognitive map that requires the hippocampus, to a schematic memory that is less tied to context and based on a less integrated neural representation in extra-hippocampal structures. Though less integrated, the amount of detail in this representation can vary with a number of factors including, for example, amount and type of training, and the complexity of the environment. Of course, the finding that spatial memories can survive hippocampal damage is also consistent with the predictions of SCT. However, to account for all of the village data, SCT would have to be modified to explain the important differences between the pre-operatively formed spatial memories involving the hippocampus and the post-operative memories that guided behaviour in the absence of the hippocampus. Moreover, the similarities in the pattern of performance of rats that were exposed to the environment before or after hippocampal lesions, suggest that the extra-hippocampal representations is the same regardless of whether they were acquired incidentally after extensive experience prior to hippocampal lesions or laboriously after hippocampal lesions.

The time it takes to form these schematic memories likely differs depending on their complexity and the species involved. In humans, it takes between 6 months to a year to form a working representation of a complex, large scale environment. In rats, daily exposure for a few weeks may suffice. Studies of contextual, spatial memories not used for navigation, but which act as associative cues for other stimuli, suggest that to develop a schematic memory, it is sufficient to have a single exposure, followed by a period of 1–4 weeks without experiencing that environment.

How quickly memories of events occurring in specific locations become independent of the hippocampus also seem to be determined by the availability of a well-formed spatial schema. Tse et al. (2007) showed that the memory of flavour-place associations could be acquired in one trial and become independent of the hippocampus within 48 h, if a well-developed spatial schema was already in place, but it took much longer, or could not be retained at all no matter when the hippocampal lesion was made, if the schema was not available. Although Tse et al. (2007) interpret these findings as supporting a rapid, systems-level consolidation account, the transformation hypothesis can explain these results just as easily. To distinguish between the different interpretations, it would be necessary to show that the rapidly assimilated memory has features in common with the schematic, spatial memories we have described rather than with the more detailed, integrated hippocampal memories on which they were initially dependent, and from which the schematic memories were derived.

1.5.1. Summary

Taken together the results of spatial memory studies refute SCT on two grounds: (1) hippocampal and extra-hippocampal spatial memories are fundamentally different from one another, and (2) this difference is evident whether the memories were acquired before or after the hippocampal lesions were made. The results support cognitive map theory insofar as showing that only the

[3] The hippocampal group's impairment on the blocked-route task appears inconsistent with Rosenbaum et al.'s (2000) report of excellent performance by patient KC when required to find a secondary route to a location after encountering a barrier along the preferred route. However, there are many differences between the tasks, the circumstances under which they were acquired, and the cognitive capabilities of humans and rats that may have accounted for some inter-species differences in the surviving memories. These differences need to be investigated before it can be concluded that animal and human findings are in conflict.

elements of hippocampus-based, allocentric spatial representations are fully integrated with one another; the extra-hippocampal schematic representations are not, though they may be sufficient to support navigation guided by allocentric cues under many conditions. The transformation hypothesis is also supported by evidence showing that memories of one type are transformed into the other by extensive experience.

1.6. The neural bases of transformed/consolidated memories

Although SCT and the transformation hypothesis take different positions regarding the reorganization of hippocampus-based memories, they agree on the point that cortical plasticity is fundamental to the long-term representation of such memories. Without necessarily specifying the nature of long-term memories under study, several experimenters, using a variety of behavioural tasks and imaging techniques, have investigated possible neural sites that are implicated in long-term and remote memories, and a number of candidate structures have emerged.

In one of the first studies to address this issue, Bontempi, Laurent-Demir, Destrade, and Jaffard, 1999 trained mice on a spatial discrimination task and tested their memory 5 or 25 days following acquisition. They also measured (^{14}C) 2-deoxyglucose uptake to map regional metabolic activity that corresponded to performance during recent and remote memory testing. The results showed an increase in hippocampal activity following acquisition and the 5-day test, but a subsequent decline at the 25-day test. Conversely, the opposite pattern was detected in frontal and temporal cortices, as well as the anterior cingulate cortex (ACC). In follow-up work, Maviel, Durkin, Menzaghi, and Bontempi (2004) confirmed these findings using a similar spatial memory task and activity-dependent gene expression of *Zif268* induced by memory processing, and added the retrosplenial cortex to the list of cortical structures potentially implicated in long-term memory (see Fig. 4). As part of that series of studies, the authors infused the anesthetic, lidocaine, into specific brain areas during memory testing to assess the effects of regional inactivation on memory performance. As predicted by the gene expression results, inactivating the hippocampus and related structures disrupted performance at short, but not long, delays. The opposite pattern was observed following inactivation of the prefrontal cortex or ACC.

Frankland and his colleagues (Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004; Frankland, O'Brien, Ohno, Kirkwood, & Silva, 2001) have taken a similar approach with respect to contextual fear conditioning. These authors tracked the expression of genes (Zif268 and c-fos) in hippocampus and cortical structures during recall of the contextual fear response at short and long delays. In line with Bontempi's results, at short delays they found increased hippocampal activity relative to that seen in the ACC and prefrontal cortex, and the opposite pattern at long delays. The importance of the ACC in long-term contextual fear memory was reinforced in this research by the inclusion of α-CaMKII$^{+/-}$ mutant mice that typically show normal learning on hippocampal-dependent tasks. These mice proved to be normal in all respects following the short-delay test of contextual fear memory, but exhibited less contextual fear and a significant reduction in gene activity in the ACC at long delays.

Takehara, Kawahara, and Kirino (2003) investigated this issue in trace eye-blink conditioning, a hippocampal dependent-task that yields temporally graded RA following lesions to the hippocampus. In their study, different groups of rats received lesions to the hippocampus, cerebellum, or medial prefrontal cortex, at different delays after training. At short delays only hippocampal and cerebellar lesions produced a reduction in the conditioned response. As the interval between training and surgery increased, the effects of the hippocampal lesion decreased, while frontal lobe lesions increasingly disrupted memory for the learned response. Cerebellar lesions impaired performance regardless of the length of the training-surgery interval. The results point to a time-limited role for the hippocampus in memory for yet another behavioural response, while providing further evidence of selective involvement of the prefrontal cortex in long-term memory representation. In line with these results, the same group provided evidence that long-term memory of the conditioned response requires activation of the prefrontal cortex to ensure successful establishment of the remotely acquired memory in this cortical region (Takehara, Nakao, Kawahara, Matsuki, & Kirino, 2006).

It follows that increases in cortical activity that correspond to the expression of remote memory would be accompanied by morphological changes in the same regions. Research in this area is in its early stages but evidence to date suggests that this is the case. In a recent study, Restivo, Vetere, Bontempi, & Ammassari-Teule (2009)

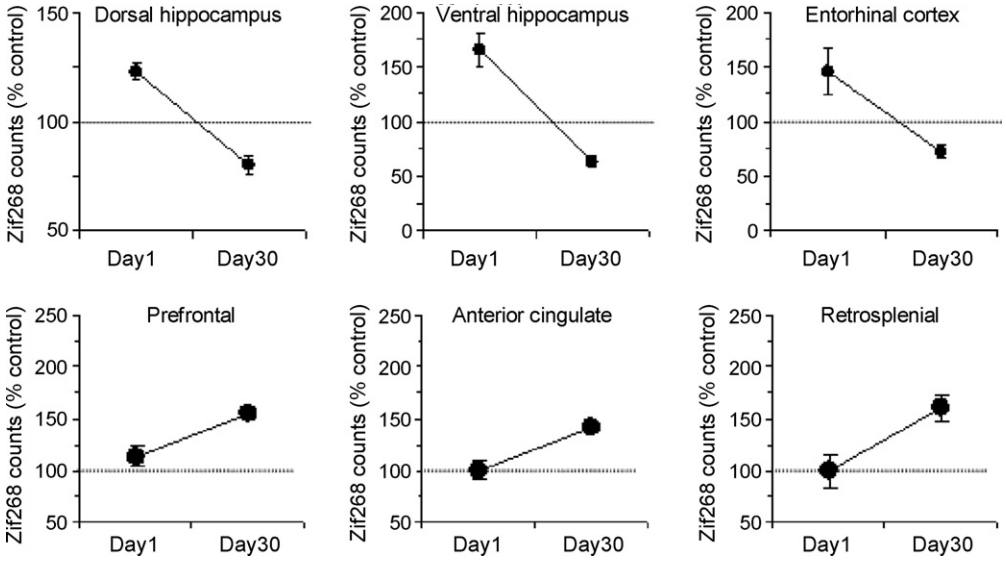

Fig. 4. Gene expression reflecting activity in medial temporal lobe (MTL) and cortical structures during tests o f spatial memory at short and long delays. Activity levels in MTL structures were higher at short, than long, delays whereas the opposite pattern was observed in cortical structures.
From Maviel et al. (2004).

measured dendritic spine growth in the hippocampus and ACC of rats 24 h or 36 days after contextual fear conditioning. Rats exhibited strong conditioned fear at both delays, but over time there were clear differences in the pattern of synaptic growth in the two structures. At short delays, there was a significant increase in spine density in sampled hippocampal (CA1) neurons that was not seen following a long delay, whereas the opposite effect was observed in ACC. The investigators also found that hippocampal lesions, produced immediately after training, eliminated the contextual fear response and prevented spinal growth in ACC, whereas no such effect was observed if the lesion was made 24 days after training. In addition to demonstrating structural changes that correspond to the formation of early and late memories, this study points to a dynamic interaction between hippocampal and cortical networks in which the hippocampus plays a crucial, but time-limited role in driving structural plasticity in the ACC.

We have begun to explore the long-term cortical sites of preserved spatial memory in our village environment. Following the lead of the above studies, as a first test we decided to investigate the possible involvement of the ACC. Our preliminary results indicate that lesions to the ACC, like the hippocampus, have little or no effect on spatial memory acquired during extensive preoperative rearing in the village. However, combined lesions to the ACC and hippocampus that prevented either structure from supporting recall did eliminate memory for learned reward locations. This research, which focuses on well-established pre-morbid memories and differs in many respects from the other studies reviewed in this section, provides further evidence that the ACC plays a critical node in a distributed cortical network involved in the reorganization of brain circuitry during the formation of long-term memories.

As already indicated, a central feature of both SCT and the transformation hypothesis is that neocortical structures are involved in the long-term representation of memories that initially form in the hippocampus, although the two approaches offer different interpretations of these representations. SCT holds that neocortically based memories are identical to those originally expressed in the hippocampus, whereas the transformation hypothesis argues that they are schematic versions of the original memories with different characteristics. The investigations of time-dependent structural and functional changes over the course of memory stabilization offer an exciting approach to informing this issue. Because none of the above studies applied tests that could determine whether the hippocampal or cortical memories were context-specific or schematic, further research is needed, particularly into the nature of the memories at short and long delays, before interpreting such evidence in terms of one theoretical position or another.

There is one consistent finding from this line of research that, on the surface at least, appears to support SCT. That is, as functional activity and structural growth begin to increase in cortical regions as long-term memories form, the same activities seen earlier in hippocampus show a decrease. This could be interpreted as a phasing out of hippocampal involvement in memory expression at long delays. However, there are unresolved issues that preclude such an interpretation at this time. For example, what is the long-term status of the structural and functional changes that took place in the hippocampus? If the hippocampus continues to be active post-conditioning, as some have shown (Hoffman & McNaughton, 2002; Walker, Brakefield, Hobson, & Stickgold, 2003), it follows that the hippocampus, in certain circumstances, might indeed have a role to play in long-term retrieval. Reduced activity and structural growth may signify partial forgetting of contextual details, but against a background of increased hippocampal activity relative to baseline, through effective cuing it may be possible to recreate conditions for rapid hippocampal engagement and the recall of hippocampally based memories. The reinstatement of memories, as seen in tests involving the reconsolidation paradigm (see above) may be an instance of this effect.

Another possibility is that reduced activity in the hippocampus may be the result of an inhibitory influence exerted by the cortical, schematic memory. (The inverse effect was suggested above with respect to reactivation of the hippocampus-based memory in our reactivation study). Admittedly, this is a speculative idea, but it receives support from unpublished preliminary work by Bontempi and his colleagues. These investigators found that, at long delays, the hippocampus is no longer engaged in remembering locations in a 5-arm spatial maze. However, when the prefrontal cortex, one of the structures implicated in long-term spatial memory (Maviel et al., 2004), is inactivated during remote memory testing, there was a marked reactivation of the hippocampus which appeared to support performance. Ongoing research is assessing the generality of this effect with respect to other structures and other tasks.

Another question relates to task demands. If, at long delays, the dominant memory for a particular task is schematic or context-general, and the cues at retrieval signal that type of memory, it follows that neocortical structures are more likely to be engaged than the hippocampus. Under such conditions, more activity in neocortical networks, as has been reported, would be expected. However, if the task were framed in such a way as to target the context-dependent, episodic version of that memory, one might expect hippocampal engagement and increased activity in that structure. That appears to be the case in functional neuroimaging studies of long-term and remote memories in humans (e.g., Trinkler, King, Doeller, Rugg, & Burgess, 2009). This question has not been investigated systematically in animals, but evidence from Bontempi's lab offers support for this scenario. In this study (Alaux et al., 2007), mice were pre-operatively trained on one of two spatial discriminations, both of which are hippocampally dependent during original learning, but vary in terms of complexity. Following training to an established criterion, hippocampal lesions or pharmacological inactivation at the time of remote memory retrieval disrupted memory for the complex task, which presumably continued to be context-dependent, but not for the less complex task, which may have developed into a schematic version that was less dependent on the training context. Significantly, when gene expression was monitored in normal mice, at long delays performance of the complex spatial task was accompanied by high levels of hippocampal activity, relative to neocortical structures, whereas the opposite pattern was observed for the less complex task.

Although this pattern of results is consistent with predictions based on the transformation hypothesis, there are different ways of explaining the permanent involvement of the hippocampus in long-term memory storage. One is that the hippocampus might remain necessary for successful performance during spatial discrimination (i.e., constant updating of the animal's spatial position as it explores the maze), or expression of an otherwise intact memory trace most likely stored in cortical areas (Broadbent, Squire, & Clark, 2006). Another possibility is that the engagement of the hippocampus at the time of remote memory retrieval is a function of the status of pre-existing knowledge in the cortex, a parameter which seems to modulate actively the rate of cortical transfer during systems consolidation (Takashima et al., 2009; Tse et al., 2007).

1.6.1. Summary

Research aimed at identifying the cortical structures that are implicated in the representation of long-term memories is in its early stages. However, available evidence, involving gene expression and imaging techniques, as well as a variety of behavioural tasks, suggests that the prefrontal cortex, anterior cingulate, and retrosplenial cortices, are amongst those that are likely involved. At this point, research in this area can be found in support of both

SCT and the transformation hypothesis and a conclusive statement must await further research.

1.7. Conclusions and implications

We identified four essential premises that form the basis of SCT in systems-level memory consolidation. (1) The central premise of SCT is that the hippocampus plays a time-limited role in the formation of long-term declarative memories by strengthening connections in neocortex where the memories are ultimately represented. The finding of temporally graded RA provided strong support for this position. (2) The same consolidation processes apply to all declarative memories, whether episodic/contextual or semantic/schematic. (3) Memories which are consolidated in neocortex are identical to preconsolidated memories which, initially, were dependent on the hippocampus. (4) Once consolidated, long-term memories are permanent in the sense that they can no longer be affected by lesions, or other amnestic agents that disrupt hippocampal function.

In evaluating these claims, we found a remarkable correspondence between the human and animal literatures if we make allowances for considering context-specific and context-general or schematic memories in animals to be the animal homologue of episodic and semantic memory, respectively, in humans. Our review of the animal and human literatures challenged each of the four premises above as follows: (1) There are as many reports of ungraded RA as there are of temporally graded RA. (2) Whereas both episodic and semantic memories may initially rely on the hippocampus, there is considerable evidence that episodic memories continue to do so for as long as they exist. In contrast, semantic memories derive from episodic memories and become represented outside the hippocampus. Semantic memories may also form independently of the hippocampus and in its absence. (3) Memories initially dependent on the hippocampus are fundamentally different from those represented ultimately outside the hippocampus. Thus, even on tasks in which a temporally graded RA is observed following hippocampal lesions, we showed that initially the memories were context-specific and mediated by the hippocampus, whereas later, the memories were less tied to context and mediated by extra-hippocampal structures. The type of memory mediated by extra-hippocampal structures is the same regardless of whether it was formed with the help of the hippocampus or without it. For each of the above instances, the functional neuroimaging literature in humans is consistent with data from lesion studies. (4) Consolidation is not permanent. Even after memories are believed to be represented in neocortex, a reminder can once again make these memories vulnerable to disruption or loss. We showed that this effect can be attributed to the reinstatement of a context-specific, hippocampus-dependent memory, but not to the activation of a context-general, neocortical memory.

These findings undermine the core of SCT that memory formation and storage is a unitary, linear process in which an engram is merely reinforced and strengthened by the hippocampus, so that, ultimately, hippocampal connections can be replaced by neocortical ones. The engram is invariant throughout this process and can be likened to moving a bit of information from one storage compartment to another. As an alternative, we have proposed a transformation model that takes into account the dynamic changes that a memory undergoes with time and experience. Contrary to SCT, this model dispenses with the notion of an invariant engram and proposes, instead, that initially formed context-specific memories can give rise to related memories that have different characteristics. In particular, in this review we focused on the transformation of episodic memories to less integrated and detailed schematic memories that capture the gist of the original. Another crucial feature of this model is that the nature of the respective memories is determined by the structures that mediate them. Thus a hippocampus-based memory is necessarily episodic and context-specific, whereas neocortex-based memories are schematic or semantic, and context-independent.

While we recognize that contextual details that comprise episodic memories are vulnerable to forgetting, leaving only the gist of the memory intact, the model allows for the possibility that some episodic memories can survive and co-exist with schematic memories. In short, contrary to SCT, the formation of hippocampus-independent memory does not necessarily entail the loss of hippocampal memories.

Yet another fundamental difference between SCT and the transformation hypothesis is that SCT places most of the burden of memory processing on encoding and storage, with retrieval relegated to the relatively minor role of providing cues to recover the engram. By comparison, the transformation hypothesis considers retrieval processes to be dynamically implicated in memory recovery and expression. In other words, memory is not simply the elicitation of an engram by cues, but rather the type of memory that is expressed emerges from the synergistic interaction of cues with stored information (see Tulving, 1983). In this sense, memory is not simply reproduced, but is reconstructed from the information that is stored on the basis of available cues, task demands, and at least in the case of humans, current motives and biases (Bartlett, 1932). In situations where two or more memories can potentially be reconstructed, the memory that is expressed is determined by the availability of the stored information, the cues that are present, and the demands of the particular task. It is only thorough the interaction of these various factors that a memory takes its particular form. This view, consistent with the transformation hypothesis, not only accounts for the reminder effect in the reconsolidation paradigm, but also for the myriad examples of memory distortion that are a common occurrence in everyday life, as well as other well-documented instances (e.g., Loftus, 2003).

Although this paper has emphasized studies of retrograde memory, it is important to note that the transformation hypothesis is consistent with a growing literature on anterograde memory on the distinction between episodic/context memory and semantic/schematic memory and their neural correlates. Recent reviews by Eichenbaum et al. (2007), and by Diana, Yonelinas, and Ranganath (2007) show that episodic memories in humans mediated by recollective processes are associated with hippocampal activation and affected by hippocampal damage, whereas semantic-like memories, mediated by familiarity processes, are associated with activation of perirhinal and other neocortical structures and affected by damage to them. Similar evidence is presented regarding context-dependent and schematic memories in rodents and other non-human animals.

There is currently vigorous debate about the nature of anterograde and retrograde memory, consolidation, and the neural processes that mediate them, from the molecular to the systems level. The introduction of new theories to challenge the standard models has stimulated intense research which will advance the field no matter which theory prevails. What is encouraging about our approach is that it allows for a unified theory of anterograde and retrograde, episodic and semantic memory, in humans and animals.

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