Neurobiology of Learning and Memory 106 (2013) 351–364

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Review

Factors affecting graded and ungraded memory loss following hippocampal lesions

Gordon Winocur [a,b,c,*], Morris Moscovitch [a,d,e], Melanie J. Sekeres [a]

[a] Rotman Research Institute, Baycrest Centre, Toronto, Canada
[b] Department of Psychology, Trent University, Peterborough, Canada
[c] Departments of Psychology and Psychiatry, University of Toronto, Toronto, Canada
[d] Department of Psychology, University of Toronto, Toronto, Canada
[e] Department of Psychology, Baycrest Centre, Toronto, Canada

ARTICLE INFO

Article history:
Received 10 May 2013
Revised 4 September 2013
Accepted 1 October 2013
Available online 9 October 2013

Keywords:
Hippocampus
Remote memory
Temporally-graded
Non-graded retrograde amnesia

ABSTRACT

This review evaluates three current theories – Standard Consolidation (Squire & Wixted, 2011), Overshadowing (Sutherland, Sparks, & Lehmann, 2010), and Multiple Trace-Transformation (Winocur, Moscovitch, & Bontempi, 2010) – in terms of their ability to account for the role of the hippocampus in recent and remote memory in animals. Evidence, based on consistent findings from tests of spatial memory and memory for acquired food preferences, favours the transformation account, but this conclusion is undermined by inconsistent results from studies that measured contextual fear memory, probably the most commonly used test of hippocampal involvement in anterograde and retrograde memory. Resolution of this issue may depend on exercising greater control over critical factors (e.g., contextual environment, amount of pre-exposure to the conditioning chamber, the number and distribution of foot-shocks) that can affect the representation of the memory shortly after learning and over the long-term. Research strategies aimed at characterizing the neural basis of long-term consolidation/transformation, as well as other outstanding issues are discussed.

1. Introduction

In this paper, we continue the debate over the role of the hippocampus (HPC) in remote memory (see reviews by Moscovitch et al., 2005; Squire & Wixted, 2011; Sutherland & Lehmann, 2011; Sutherland et al., 2010; Winocur, Moscovitch, & Bontempi, 2010; see also overview by Dudai, 2012). Much of this debate has centred on whether HPC lesions lead to non-graded retrograde amnesia (RA) (Sutherland & Lehmann, 2011; Sutherland et al., 2010) or a graded effect in which old memories are preserved (Squire & Wixted, 2011). Our position is that both patterns are possible depending on the demands of the task, and by inference, the nature of memory representations that support performance (Moscovitch et al., 2005; Winocur et al., 2010). Readers will note some overlap with previous reviews. This was necessary to contextualize issues over which there is theoretical disagreement as well as to introduce discussions of factors that may affect memory representations but have received less attention in the literature. The focus here is on rodent research where there have been significant advances in recent years. At the same time, parallel issues emerging from studies of RA in humans (see Winocur & Moscovitch, 2011) converge with those addressed here, and a full understanding of HPC involvement in remote memory will depend ultimately on the resolution of outstanding issues across the species.

2. HPC and remote memory: theoretical perspectives

In the 1950s, Milner and her colleagues discovered that, in addition to a profound anterograde amnesia (AA), the classic bitemporal patient, H.M., as well as other patients with similar damage to the HPC and medial temporal lobes, exhibited a temporally-graded retrograde amnesia (TGRA) that was characterized by a severe loss of memory for events experienced shortly before surgery, but preserved memory for older experiences (Penfield & Milner, 1958; Scoville & Milner, 1957). This seminal work, which established the HPC as a critical structure in the mediation of memory, was interpreted in terms of what was to become the standard consolidation theory (SCT). According to this view, retention and retrieval of long-term memories initially rely on the medial temporal lobes, particularly the HPC, which provide an index or pointer to neocortical structures in which the content of the memory is represented (Teyler & DiScenna, 1986). With time and experience, and HPC modulation, the cortico-cortical connections are strengthened to

* Corresponding author. Address: Rotman Research Institute, Baycrest Centre, 3560 Bathurst Street, Toronto, Ontario M6A 2E1, Canada. Fax: +1 (416) 785 2474.
E-mail address: gwinocur@research.baycrest.org (G. Winocur).

1074-7427/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nlm.2013.10.001

the point that they can support long-term memory without HPC involvement, a condition that marks the end of the consolidation process. A default assumption of this view, made by subsequent investigators, is that memory remains virtually unchanged. Interestingly, Penfield and Milner (1958) speculated on the possibility that the nature of the memory representation might undergo changes during the consolidation process. When interpreting the effects of medial temporal lobectomy, they proposed that "The record of the stream of consciousness which, we believe, depends upon the integrity of the hippocampal structures, cannot be called into activity voluntarily except for a relatively short period of time [after acquisition]" (pp. 493–495). Thereafter, only a generalized version of that record could be accessed without HPC involvement.

With the development of appropriate paradigms, investigators showed that lesions restricted to the HPC interfered with the formation of new memories in rodents (e.g., Winocur & Olds, 1978) and sub-human primates (Zola-Morgan & Squire, 1985), but it was not until the 1990s that the effects of such damage on retrograde memory was investigated in animal models. One paradigm involved a test of socially-acquired food preferences, in which a subject (***S***) animal is paired with a demonstrator (***D***) animal that has recently eaten distinctively flavoured food. By interacting with ***D***, ***S*** learns to prefer that food over other flavoured foods that they have not experienced previously (Galef, Kennett, & Stein, 1985). A second paradigm utilized contextual fear conditioning. In the conventional version of this task, a fear response (freezing), created by foot shocks administered in a conditioning environment, becomes associated with the array of contextual cues that comprise that environment (Fanselow, 1990).

Initial studies showed that rodents with HPC lesions display TGRA on both tasks (food preference – Winocur, 1990; contextual fear conditioning – Kim & Fanselow, 1992) and, in the process, reinforced SCT as the definitive statement of HPC function in memory. However, conflicting results emerged from studies using tests of allocentric spatial memory which required animals to learn and remember a specific location in relation to a configuration of distal environmental cues. In a variety of water- and land-based tasks that made similar demands, animals with HPC lesions were found to be severely impaired in learning new locations (Morris, Garrud, Rawlins, & Okeefe, 1982; Olton, Becker, & Handelmann, 1979) and in retrieving pre-operatively acquired spatial memories, regardless of the training-surgery interval (Clark, Broadbent, & Squire, 2005b; Martin, de Hoz, & Morris, 2005; Sutherland et al., 2001; Winocur, Moscovitch, Caruana, & Binns, 2005).

Evidence that lesions to the HPC system can produce both graded and non-graded RA, which is also found in the human literature (Cermak & O'Connor, 1983; Marslen-Wilson & Teuber, 1975; Poreh et al., 2006; Rosenbaum, Gilboa, Levine, Winocur, & Moscovitch, 2009; Steinvorth, Levine, & Corkin, 2005), was related to considerable research that highlighted the existence of multiple forms of memory, each with its own characteristics and underlying neural system (O'Keefe & Nadel, 1978; Tulving, 1985). In turn, this raised the possibility that the two patterns of RA that had been associated with HPC damage reflected different testing methods that assessed different types of memory. As an alternative to SCT, Nadel and Moscovitch (1997) proposed Multiple Trace Theory, based on Moscovitch's (1992) component process model of memory.

MultipleTrace Theory posits that the HPC binds together the neocortical neural elements that mediate the conscious experience of an episode, thereby forming a memory trace that consists of an ensemble of HPC-neocortical neurons. Each time an episodic memory that captures the event is retrieved, it is re-encoded automatically by the HPC along with the new context in which the retrieval occurs. Over time and successive retrieval episodes, multiple memory traces of the event accumulate. Concurrently, the neocortex extracts the statistical regularities across these representations to capture the general features of the event (semantic memory), without the contextual richness that gives them their (unique) episodic character. By this view, insofar as memories remain episodic, they always will be dependent on the HPC. In contrast, semantic memories that are mediated by the neocortex can be recovered without HPC involvement.

The distinction between episodic and semantic memory, and its relevance for consolidation, was elaborated further by the Transformation Hypothesis (Winocur & Moscovitch, 2011; Winocur et al., 2010). According to this hypothesis, diminished HPC involvement and reliance on extra-HPC structures for retention and retrieval is associated with a transformation process that results in a schematic version that captures the gist of the initial episodic memory. This can be accomplished either by the extraction of statistical regularities over repeated retrieval episodes, as proposed by Multiple Trace Theory, or by retaining only the essential elements of the experience without those that define its uniqueness. In either case, a schematic memory lacks the contextual richness that is the hallmark of the initial episodic memory representation. Once formed, the schematic memory can exist concurrently with the episodic memory, or by itself, if the episodic memory trace is degraded through forgetting and decay. It is also the case that a schematic representation can facilitate the formation, retention and retrieval of episodic memories that are related to the schema. Thus, at the heart of the Transformation Hypothesis, is the notion of a dynamic interplay between the HPC and extra-HPC structures during formation and expression of two different memory representations, one contextually rich and specific, and the other more schematic and contextually impoverished.

The Transformation Hypothesis carries with it the following implications: (1) The representations of HPC-dependent and independent memories are not copies of one another; their representations are quite different. (2) HPC memories are distinguished by their rich, contextual specificity. (3) Memories that retain their context-specificity always depend on the HPC, no matter how long ago they were formed, making them always vulnerable to HPC damage. (4) By contrast, schematic, gist-like or semantic memories can exist independently of the HPC, as can all manner of non-declarative memories, making them resistant to HPC damage, but susceptible to extra-HPC damage. TGRA that is observed on some tasks (e.g., contextual fear conditioning, socially-acquired food preference) following HPC disruption occurs because shortly after acquisition, the memory is rich and context-specific, making it susceptible to HPC disruption, but with time and/or experience that memory is transformed to a schematic version that is HPC-independent. (5) The two types of memories, detailed context-specific memories and gist-like schematic memories, can co-exist, and complement each other or compete with one another. Thus, HPC lesions or inactivation, may lead to loss of episodic memories while leaving neocortical schematic memories intact, whereas the reverse can occur with some extra-HPC disruption. (6) Under proper conditions, the dominance of one or the other memory can be altered. Reinstating a rich, context specific representation when previously an impoverished schematic memory was predominant, will also reinstate HPC-dependence, and render the memory vulnerable to HPC disruption.

A third account of HPC function in remote memory, advanced by Sutherland et al. (2010), is also based on the notion of multiple memory systems. According to this view, memories can be acquired through a variety of systems, but in the normal brain the HPC system typically is dominant and, when recruited for new learning, overshadows and suppresses the participation of other systems. A central premise of what can be termed 'Overshadowing Theory' is that brain regions in other, less efficient, systems can take over in new learning if the HPC is damaged before the task is presented.

However, HPC lesions will produce widespread amnesia for pre-operatively acquired information. Although there appears to be no system that compensates for the devastating effects of HPC lesions on new spatial learning, Overshadowing Theory can explain the non-graded RA that is associated with HPC lesions on spatial tasks. As noted by Sutherland et al. (2010), the theory is also supported by evidence of non-graded RA on other tasks (Broadbent, Squire, & Clark, 2007; Gaskin, Tremblay, & Mumby, 2003; Lehmann, Lecluse, Houle, & Mumby, 2006; Sutherland et al., 2001), but not by the consistent reports of TGRA on the socially-acquired food preference task.

A major source of support for SCT, Multiple Trace-Transformation (MT-T), and Overshadowing Theories derives from the findings of studies of contextual fear conditioning. However, here the theories draw support from conflicting results. The SCT and MT-T accounts are consistent with studies showing TGRA for contextual fear following HPC lesions, whereas several reports of non-graded RA are taken as support for Sutherland et al.'s position. The apparent contradiction in the contextual fear literature has contributed significantly to the persistent theoretical differences in this area and it is important to resolve them. With that in mind, the following section reviews that literature and explores factors that may help to explain the contradictory findings.[1]

3. Agreements and disagreements

Proponents of the various theories do not necessarily interpret results in the same way but, as noted above, there is broad agreement regarding the effects of HPC damage on two of the most commonly used tasks to assess remote memory in animals. Since Winocur's initial demonstration in 1990, numerous studies have utilized the socially-acquired food preference task and, with one exception (Burton, Murphy, Qureshi, Sutton, & O'Keefe, 2000), all reported TGRA in HPC groups (e.g., Alvarez, Wendelken, & Eichenbaum, 2002; Bunsey & Eichenbaum, 1995; Clark, Broadbent, Zola, & Squire, 2002; Squire & Alvarez, 1995; Winocur, McDonald, & Moscovitch, 2001). There is similar consistency regarding conventional tests of spatial memory (e.g., water maze, cross-maze). The great majority of studies using these tasks reported non-graded RA, even at very long training-surgery intervals (e.g., 100 days – Clark et al., 2005b; 6 months – Clark, Broadbent, & Squire, 2005a; Winocur et al., 2005; see Ramos, 1998, for a rare exception). HPC lesions also produce reliable deficits on new spatial learning and memory (Morris et al., 1982; Olton et al., 1979). Ironically, the consistent results emanating from studies using food-preference and spatial memory tasks have contributed to a theoretical conundrum. Overshadowing Theory, which predicts a flat gradient for all tests, is challenged by the reliable finding that HPC lesions produce TGRA for learned food preferences, while the non-graded RA that is typically seen on spatial memory tests runs counter to SCT, which predicts TGRA in all cases. MT-T Theory, as discussed below, allows for the possibility of both types of gradients depending on the nature of the task and the memory representation that supports performance.

The contextual fear literature poses problems for all three theoretical positions because of conflicting results. As can be seen in Table 1, since Kim and Fanselow (1992) first reported that HPC lesions produce TGRA of a contextual fear response, there have been numerous replications of this finding. At the same time, investigators have also reported non-graded RA on this task. The graded effect is not predicted by Overshadowing Theory while the non-graded effect is inconsistent with SCT. MT-T Theory can account for both types, but only if the two patterns can be shown to reflect different types of memory, one that is context-specific and the other, context-general. Contextual fear conditioning has also been used extensively to test anterograde memory and, here again, in contrast to studies utilizing the food-preference and spatial memory tests, the effects of disrupting HPC function through lesions or inactivation techniques are inconsistent (see Table 2).

There are a number of factors that could account for the discrepancies in the HPC contextual fear conditioning literature. Among them are lesion size, and several procedural factors that include the complexity of the contextual environment, amount of pre-exposure to the conditioning chamber, and various shock parameters (intensity, number, duration and distribution), all of which can determine or influence the characteristics of the memory at different intervals after acquisition. We review these in the following section.

4. Factors affecting learning and memory of a contextual fear response

4.1. Lesion size and location

Studies of the effects of HPC lesions on contextual learning and memory vary considerably in terms of extent and location of damage. In several studies of contextual fear conditioning, Winocur and colleagues made large hippocampal lesions that included dorsal and ventral regions and affected as much as 100% of the HPC. Such lesions resulted in impaired learning of a contextual fear response (Winocur, Moscovitch, & Sekeres, 2007; see also Kjelstrup et al., 2002; Richmond et al., 1999) and TGRA when the response was pre-operatively learned (Winocur, Frankland, Sekeres, Fogel, & Moscovitch, 2009; Winocur, Sekeres, Binns, & Moscovitch, 2013). In Winocur et al.'s studies, lesions were restricted to the hippocampus and the behavioural results were unrelated to the size of the lesion. Sutherland, Lehmann, and colleagues varied the size and location of HPC lesions in two investigations of remote contextual fear memory (Lehmann, Lacanilao, & Sutherland, 2007; Sutherland, O'Brien, & Lehmann, 2008). In contrast to Winocur et al.'s results, each type of lesion produced non-graded RA with the severity of the amnesia increasing with the extent of damage. Importantly, there was no evidence of spared remote memory or TGRA in rats that had sustained relatively small HPC lesions.

It is not surprising that large brain lesions sometimes cause more severe learning and memory deficits than small lesions. The important finding is that there is little evidence that variations in HPC lesion size can explain the inconsistent results regarding the pattern of lost and spared contextual learning and memory. With respect to retrograde memory, we concur with Sutherland et al. (2010) who concluded that "the extent of damage to the HPC is not an important factor in determining whether a temporal gradient is observed," (p. 2360).[2]

With respect to lesion location, Fanselow's group typically makes restricted lesions to the dorsal HPC. On tests of retrograde memory, their consistent finding is lesion-induced TGRA (e.g., Kim & Fanselow, 1992; Kim, Rison, & Fanselow, 1993; Quinn, Ma, Tinsley, Koch, & Fanselow, 2008). On tests of anterograde memory,

[1] SCT, MT-T, and Overshadowing Theories do not exhaust the list of theoretical positions regarding the role of the HPC in memory (see, for example, Eichenbaum & Cohen, 2001; Gluck & Myers, 1993). They are the focus in the present review because, as indicated earlier, they have been featured in recent theoretical discussions (Winocur, Moscovitch, & Bontempi, 2010; Sutherland & Lehmann, 2011; Sutherland et al., 2010). As well, they are central to the debate with respect to remote memory, and speak directly to the controversies associated with contextual fear conditioning. One prominent theoretical notion is Schema Assimilation (Tse et al., 2007). However, we do not consider Schema Assimilation as an alternative theory, but one of the means by which memories are transformed (see discussion below).

[2] This contrasts with statements made in the initial iteration of MTT, which posited that size of a medial temporal lobe lesion (not restricted to the HPC) determined the extent of RA.

Table 1
Studies demonstrating temporally-graded or non-graded retrograde amnesia of a conventional contextual fear response in animals with HPC damage.

Temporally-graded		Non-graded	
Authors	HPC disruption	Authors	HPC disruption
Kim and Fanselow (1992)	Electrolytic lesion	Lehmann et al. (2007)	NMDA lesion
Maren et al. (1997)	NMDA lesion	Sutherland, O'Brien, and Lehmann (2008)	NMDA lesion
Anagnostaras et al. (1999)	Electrolytic lesion	Lehmann et al. (2009)[a]	NMDA lesion
Frankland et al. (2006)	Anisomycin	Sparks, Lehmann, Hernandez, and Sutherland (2011)	NMDA lesion
Quinn, Ma, et al. (2008)	NMDA lesion	Lehmann, Rourke, Booker, and Gleen (2012)	NMDA lesion
Kitamura et al. (2009)	Irradiation		
Wang et al. (2009)	NMDA lesion		
Winocur et al. (2009)	NMDA lesion		
Wiltgen et al. (2010)	CNQX		
Corcoran et al. (2011)	APV		
Winocur et al. (2013)	NMDA lesion		

[a] Single conditioning session produced RA in HPC-lesioned rats. Multiple sessions did not.

Table 2
Studies demonstrating normal or impaired acquisition of a conventional contextual fear response in animals with HPC damage.

Deficit		No-deficit	
Authors	HPC disruption	Authors	HPC disruption
Phillips and LeDoux (1992)	Electrolytic lesion	Maren et al. (1997)	NMDA lesion
Kim et al. (1993)	Electrolytic lesion	Frankland et al. (1998)	Electrolytic lesion
Phillips and LeDoux (1994)	Electrolytic lesion	Cho et al. (1999)	Ibotenic acid
Young, Bohenek, and Fanselow (1994)	NMDA lesion	Gisquet-Verrier et al. (1999)	Ibotenic acid
Maren and Fanselow (1997)	Electrolytic lesion	Shors, Townsend, Zhao, Kozorovitskiy, and Gould (2002)	Methylazoxymethanol acetate
Gerlai (1998)	Ibotenic acid	Quinn, Wied, Ma, Tinsley, and Fanselow (2008)	NMDA lesion
Rampon et al. (2000)	CA1 – Knock-out	Tayler et al. (2011)	NMDAR antagonist
Stiedl, Birkenfeld, Palve, and Spiess (2000)	NMDA lesion	Zelikowsky et al. (2012)	NMDA lesion
Lattal and Abel (2001)	Anisomycin		
Athos, Impey, Pineda, Chen, and Storm (2002)	APV		
Kida et al. (2002)	CREB repression		
Bast, Zhang, and Feldon (2003)	NMDA lesion, MK 801		
Fleischmann et al. (2003)	NMDAR antagonist		
Sanders and Fanselow (2003)	APV		
Frankland et al. (2004)	NMDAR antagonist		
Matus-Amat et al. (2004)	Muscimol		
Saxe et al. (2006)	Irradiation; genetic ablation		
Wiltgen et al. (2006)[a]	NMDA lesion		
Winocur, Wojtowicz, Sekeres, Snyder, and Wang (2006)	Irradiation		
Moses et al. (2007)[b]	NMDA lesion		
Wojtowicz, Askew, and Winocur (2008)	Irradiation		
Hernandez-Rabaza et al. (2009)	Irradiation		
Czerniawski et al. (2011)	APV		
Kathirvelu, East, Smith, and Colombo (2013)	Mutant CREB expression		

[a] HPC-lesioned rats acquired the fear response more slowly than controls.
[b] The severity of the deficit was related to the complexity of the context.

the results are mixed – Kim et al. (1993), and Maren and Fanselow (1997) reported deficits, whereas Maren, Aharonov, and Fanselow (1997) found no effect. In two studies, Phillips and LeDoux (1992, 1994) found that dorsal HPC lesions interfered with acquisition and recall of a contextual fear response. Other investigators found that selective disruption of the ventral HPC by lesion (Czerniawski, Ree, Chia, & Otto, 2012; Esclassan, Coutureau, Di Scala, & Marchand, 2009; Richmond et al., 1999; Trivedi & Coover, 2006) or functional inactivation (Bast, Zhang, & Feldon (2001); Zhang, Bast, & Feldon, 2001), interferes with contextual fear conditioning.

These results suggest that both dorsal and ventral regions of the HPC are implicated in contextual fear conditioning. Indeed, studies that compared the effects of selective disruption of dorsal and ventral regions on this task showed deficits in both cases (Czerniawski et al., 2012; Esclassan et al., 2009). Consistent with these reports, it has been argued that, while both regions are involved, they participate in different ways (Esclassan et al., 2009; Fanselow & Dong, 2010). The proposal is that the dorsal HPC plays a cognitive role in processing the allocentric spatial information that is relevant to learning and remembering a contextual fear response, whereas the ventral HPC is important for the affective component that mediates the fear behaviour. The latter is supported by anatomical evidence of numerous direct connections between the ventral HPC and amygdala (Pitkanen et al., 2000), a structure that is known to be involved in the expression of fear (see reviews by Maren, 2001; Poppenk, Evensmoen, & Moscovitch, 2013).

On a cautionary note, the evidence is not uniform in showing that both the dorsal and ventral HPC regions participate in contextual fear conditioning. For example, Richmond et al. (1999) reported that, while ventral HPC lesions impaired acquisition of a contextual fear response, dorsal HPC lesions did not. Kjelstrup et al. (2002), on the other hand, reported no effect of selective lesions to either HPC region, although they did find a deficit following complete lesions. Clearly, further research is needed to resolve issues of functional localization in the HPC and to determine if this is one of the factors in the discrepant results around the structure's involvement in learning and memory.

4.2. Contextual environment

The acquisition of a contextual fear response is believed to depend on the ability to combine the array of contextual cues in the conditioning environment into a configural whole, which is then associated with foot-shock. The HPC is believed to be critically important to the process of forming these configural relationships (see Fanselow, 2010; Sutherland & Rudy, 1989). It follows that the greater the number of contextual elements in the environment, the greater the burden on the HPC. Conversely, a relatively homogeneous environment, consisting of only a few distinct contextual cues that can be directly associated with shock, should pose less of a challenge to animals with HPC lesions. In fact, this appears to be the case. Moses, Winocur, Ryan, and Moscovitch (2007) administered contextual fear conditioning to normal and HPC-damaged rats in a white box with virtually no contextual variation (simple context) or in a chamber with transparent walls that was located in a standard testing room with a number of diverse contextual stimuli (complex context). HPC lesions resulted in less fear conditioning in both contexts but the effect was far greater in the complex context.

The Moses et al. (2007) study appears to be the only one to have systematically examined the effect of environmental complexity on contextual fear conditioning. However, several others that investigated related forms of contextual learning point to the same conclusion. For example, Winocur, Rawlins, and Gray (1987) showed that rats with HPC lesions were unimpaired in learning a contextual discrimination involving simple white and black boxes in which one was associated with foot-shock and the other was not. Similar results were reported by Good and Honey (1991), using an appetitive task that required rats to discriminate between two simple contexts in which only one was associated with food delivery. Interestingly, in that study, rats with HPC lesions were impaired when different conditional stimuli were added to the two contexts, thereby increasing demands on configural learning.[3] The authors concluded that the HPC is more likely to be involved in *higher order* contextual processing.

These results are consistent with other evidence from our lab (Winocur, 1997; Winocur & Gilbert, 1984; Winocur & Olds, 1978) and from other labs (Gisquet-Verrier, Dutrieux, Richer, & Doyere, 1999) that rats with HPC lesions can form contextual associations in simple environments where distinct contextual stimuli are reliably associated with reward. They also help to resolve a longstanding controversy in the literature with respect to the effects of HPC lesions on learning contextual relationships. In a series of influential papers, Hirsh and colleagues (Hirsh, 1974, 1980; Hirsh, Leber, & Gillamn, 1978) reported that HPC lesions interfered with rats' ability to learn discrimination responses on the basis of different sets of contextual cues. Hirsh attributed the deficits to a failure to use contextual cues to retrieve stored information. An important feature that distinguished Hirsh's studies is that his were conducted in complex environments that contained multiple contextual elements whereas the others were conducted in simpler environments.

The procedures described in most published reports of contextual fear conditioning do not lend themselves to reliable comparisons of environmental complexity to determine if there are significant variations in the number, type, and salience of contextual cues. Nevertheless, it follows from the available evidence and from our reasoning that the nature of the contextual environment could be a significant' factor affecting the strength of contextual fear conditioning and the representation of the fear response. Moses et al.'s (2007) results are a strong endorsement of this position but clearly more research along these lines is required.

4.3. Exposure to conditioning chamber

It has been suggested that placing the animal in the conditioning chamber for a period of time before delivering shock promotes the formation of a detailed and integrated representation of the contextual environment in the HPC and allows for contextual fear conditioning (Fanselow, 2010; Matus-Amat, Higgins, Barrientos, & Rudy, 2004; Phillips & LeDoux, 1992; Rudy & O'Reilly, 1999). When normal animals are shocked immediately upon being placed in the conditioning chamber, they do not form a contextual fear response (*immediate shock deficit* – Fanselow, 1990; see also Frankland, Josselyn, et al., 2004; Kiernan & Westbrook, 1993; Matus-Amat et al., 2004). On the other hand, following sufficient pre-exposure to the chamber, they reliably form a strong contextual fear response (*context pre-exposure facilitation effect* – Rudy, Barrientos, & O'Reilly, 2002; see also Biedenkapp & Rudy, 2007; Fanselow, 1990).

These effects have also been observed in rats with HPC lesions. Wiltgen, Sanders, Anagnostaras, Sage, and Fanselow (2006) administered foot-shock to HPC-lesioned and control groups immediately after placement in the conditioning chamber or at delays ranging between 24 and 340 s. No group acquired a contextual fear response in the 0-delay condition but, in both groups, contextual fear conditioning increased with the length of the delay. Significantly, beyond the 24-s delay, the HPC group exhibited weaker fear responses than controls. Similar results have been reported by Rudy, Barrientos, and O'Reilly (2002).

These findings have implications for the theoretical positions discussed above. Wiltgen et al.'s (2006) results could be interpreted as support for Overshadowing Theory, which maintains that following HPC lesions, contextual fear conditioning is taken over by another brain system that forms non-configural associations between discrete (elemental) stimuli and fear responses. However, as Fanselow (2010) has noted, if the HPC-lesioned animals in Wiltgen et al.'s (2006) study used such a learning strategy then, in line with findings from latent inhibition studies, *poorer* conditioning would be expected with increased pre-exposure to the context. Fanselow (2010) concluded that the HPC group engaged in an inefficient form of relational or configural learning, rather than a qualitatively different learning strategy. By this reasoning, Wiltgen et al.'s (2006) results would challenge Overshadowing Theory. SCT and MT-T Theory also allow for the existence of multiple memory systems that could perform compensatory learning functions. An alternative interpretation, in line with Fanselow's (2010) account and MT-T Theory, is that extended pre-exposure to the conditioning environment allowed for the development of a schematic representation of the context that rats with HPC lesions could use to form associations with shock. Long-term memories of the fear response acquired in this way take longer to form and differ from HPC-dependent memories in richness and contextual detail.[4]

[3] Wang, Teixeira, Wheeler, and Frankland (2009) also found normal contextual discrimination following HPC lesions. They employed a fear conditioning procedure in relatively complex environments but, in an important procedural difference (amongst several) with the Winocur et al. (1987) and Good and Honey (1992) studies, Wang et al. (2009) administered multiple context discrimination training trials distributed over several days prior to HPC lesioning, which likely contributed to the preserved discrimination of remote context fear memory.

[4] In a related series of studies, Winocur and colleagues (Winocur, Moscovitch, Fogel, Rosenbaum, & Sekeres, 2005; Winocur, Moscovitch, Rosenbaum, & Sekeres, 2010) found that rats with considerable pre-operative experience in a complex environment exhibited preserved spatial memory for that environment after receiving HPC lesions. Careful analysis of response patterns revealed that, in navigating the environment, HPC and control groups used similar spatial strategies based on forming configural relations between distal contextual cues. The major difference between the groups was that within the contextual environment, the configural relations formed by rats with HPC lesions were less detailed and integrated with each other. Consequently, the HPC rats were less efficient in their use of cues and made more errors before finding specific locations.

The *context pre-exposure facilitation effect* may be a factor in determining the gradient of RA for a contextual fear memory following HPC lesions. We have found that when rats are pre-exposed to the conditioning chamber the day before contextual fear conditioning for relatively long periods (15 min – Winocur et al., 2009; 30 min – Winocur et al., 2013), they reliably exhibit TGRA following HPC lesions. When exposure is brief (less than 5 min) as is the case in most experiments, HPC disruption can produce either graded (e.g., Corcoran et al., 2011; Frankland et al., 2006; Maren et al., 1997; Wiltgen et al., 2010) or non-graded RA (Lehmann et al., 2007; Sutherland, O'Brien, & Lehmann, 2008). This suggests that pre-exposure beyond a critical duration supports the formation of a contextually rich representation of the fear memory that is HPC-dependent and, and in our view, is a pre-requisite for initiating a transformation process. This process leads to a schematic memory that is represented elsewhere in the brain and is resistant to HPC lesions. Following short pre-exposure periods, a representation of the contextual fear response is formed in the HPC, but it may not be sufficiently detailed to initiate or support transformation. As a result this memory needs the HPC to remain viable and, therefore, vulnerable to HPC lesions even at long learning – surgery intervals. The variable results with respect to RA patterns following short pre-exposure times, may reflect differences in the animals' orientation to the chamber, in their attention to contextual features of the environment and, importantly, in the quality of the original representation which sets the stage for how memories will be represented over the short and long-term.

4.4. Effect of shocks: intensity, duration, number and distribution

Other factors that could affect acquisition of the contextual fear response and the pattern of memory loss following HPC lesions are the duration and intensity of the foot-shock, as well as the number of shocks. In most experiments, 1–2-s. shocks, ranging between 0.5 and 1.5 mA, are delivered during fear conditioning. A couple of studies varied shock intensity but the results are conflicting. Gisquet-Verrier et al. (1999) reported that increasing shock levels reduced freezing in rats with HPC lesions, while Quinn, Wied, Ma, Tinsley, and Fanselow (2008) found the opposite effect. These factors have not been examined extensively but, overall, there is little indication from a comparison across studies that, within the parameters tested, variations in shock *amplitude or duration* differentially affected freezing behaviour on tests of anterograde or retrograde memory.[5]

On the other hand, the *number* of shocks may be a factor. Wiltgen et al. (2006) showed that rats with HPC lesions were impaired in learning a contextual fear response under standard training conditions when a single 1.5 mA shock was delivered, but learned normally when three shocks were administered. It is noteworthy that long exposure times accompanied the multiple shocks so that the two factors may have combined to facilitate learning. In another study, Quinn, Ma, et al. (2008) and Quinn, Wied, et al. (2008) administered 3 or 10 foot-shocks and found that rats with HPC lesions acquired a contextual fear response as well as controls.[6] These studies show, in line with other reports (Cho, Friedman, & Silva, 1999; Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998; Maren et al., 1997) that under certain conditions, animals with HPC damage can acquire a contextual fear response normally, consistent with the view that other systems can compensate for a dysfunctional HPC (Sutherland et al., 2010). As a cautionary note, other investigators have reported that rats with HPC lesions exhibit impaired fear conditioning, even though they were administered many shocks of comparable intensity and duration during training (e.g., Maren & Fanselow, 1997; Phillips & LeDoux, 1992, 1994; Winocur et al., 2007).

If the number of shocks during training influences contextual fear learning in rats with HPC lesions, then this variable is also likely to be a factor in remote memory. To date, there is only one study that examined this directly but the findings were inconclusive. Lehmann et al. delivered 3 or 10 shocks to rats in a contextual fear conditioning session and then performed HPC or sham surgery 7, 50, or 100 days later. At the longer intervals, the HPC group that had received 10 shocks exhibited better memory of the fear response than the 3-shock HPC group, although both groups froze less than controls. The authors state there was evidence that "contextual fear memory becomes independent of the HPC over a protracted period [50 days] when acquired under strong learning parameters", but curiously, at the longest delay [100 days], the memory was lost. There appears to be no obvious explanation for this pattern of results.

The *distribution* of shock delivery appears to be a crucial factor. In a test of retrograde memory in rats, Lehmann et al. (2009) delivered multiple shocks under massed conditions in a single trial or the same number of shocks distributed over several sessions, and then performed HPC or control surgery. At test, the HPC group in the massed condition failed to exhibit a contextual fear response and, in fact, behaved like HPC-lesioned rats that received a single shock in similar experiments (Lehmann et al., 2007; Sutherland, O'Brien, & Lehmann, 2008). In contrast, the HPC group in the distributed condition showed excellent retention of the response.

In many studies that have reported preserved remote memory for a contextual fear response in HPC-damaged animals (e.g., Anagnostaras, Maren, & Fanselow, 1999; Kim & Fanselow, 1992; Wang et al., 2009; Winocur et al., 2009, 2013), the training procedure involved multiple shocks that were administered in distributed fashion or with substantial inter-trial intervals built into the training schedule. It is also noteworthy that the effect of multiple shocks is frequently confounded by the effects of increased exposure to the conditioning environment which, as discussed above, may contribute to stronger contextual fear conditioning.[7]

An important point is that even when animals with HPC lesions appear to learn a contextual fear response, there is evidence that their memory is not as durable as in normal animals. For example, in one experiment (Zelikowsky, Bissiere, & Fanselow, 2012), HPC-lesioned and control rats received contextual fear conditioning and were then tested 1, 3, 10, or 30 days later. There was no difference between the groups on the 1-day test. However, in contrast to control groups whose memory remained stable over all test intervals, rats with HPC lesions exhibited forgetting of the fear response that was apparent as early as 3 days after conditioning. Wang et al. (2009) used a contextual discrimination task and found that although mice with HPC lesions exhibited good remote memory for a pre-operatively acquired context discrimination, memory for the response was more susceptible to decay than in controls. Along the same lines, other investigators have reported that when the HPC is disrupted, animals require more fear conditioning trials than controls to reach the same level of performance (Gulbrandsen, Sparks, & Sutherland, 2013).

4.5. Accounting for discrepancies: how factors interact with each other, and with context

The preceding review suggests that insufficient attention has been paid to factors that influence acquisition and memory of a

[5] It should be acknowledged that species differences (rats vs mice) compound the difficulty in drawing comparisons across studies from different labs. A consideration of this variable, in combination with others, was determined to be beyond the scope of this paper.

[6] In that study, Quinn et al. (2008) also varied shock levels (.4–.9 mA). The higher shock level produced more freezing but neither variable selectively or in combination affected learning in HPC-lesioned rats.

[7] This was not the case in the Lehmann et al. (2009) study.

contextual fear response. In considering the various reports, we are left with the impression that the conditions associated with training play an important role in determining the contextual fear response and the pattern of RA seen after HPC lesions. What then are the optimal conditions that will support acquisition of a strong contextual fear response and the processes that will enable the response to resist the effects of HPC lesions? This is a difficult question to answer, largely because these factors undoubtedly interact with one another, and in unknown ways, so that unless ***all*** factors are manipulated in a controlled fashion, it is virtually impossible to isolate, and thereby identify, which factors influence performance. This is less of an issue when the studies are conducted in the same lab, where generally factors are held constant except the one that is being investigated. Across labs, however, there is huge potential for variation in the contextual environment, which may well be the critical element in all contextual fear conditioning paradigms. Some factors can be manipulated by systematic variation along measurable dimensions (e.g., amount of pre-exposure, intensity, number, and distribution of shocks). However, the context itself is multifactorial and can vary in terms of the shape, colour, pattern and texture of the conditioning chamber, the shape and size of the room where training and testing occur, as well as the number and type of distal stimuli distributed in the surrounding environment and their relation to each other. As indicated above, only one study (Moses et al., 2007) has attempted to manipulate context systematically, but even that one did not investigate the effect of variation within a complex context and how it may interact with the other variables.

The various factors that prevail during training impact the nature of the contextual representation that will ultimately determine whether or not it is dependent on the HPC. Thus, for example, adequate pre-exposure is needed for the animal to form a representation that is sufficiently rich in contextual associations (context-specific) to be mediated by the HPC. However, under certain conditions, increasing the number shocks, and the fear that accompanies them, may over-ride this process by constricting the animal's focus to only some simple or generalized elements of the context, resulting in a loss of context specificity and a representation that can be mediated by extra-HPC structures.

The literature on the effect of emotion on memory in humans may be instructive in this regard. In a series of experiments, Kensinger, Piguet, Krendl, and Corkin (2005) showed that when presented with a fear inducing item in a neutral context, memory for both is sometimes enhanced, but on many occasions, memory for the item is retained at the expense of memory for the context, a phenomenon termed the *emotion-memory trade off effect*. This effect is associated with activations at encoding in temporal–parietal regions that do not include the HPC.

This interpretation suggests how factors such as pre-exposure and number of shocks may interact to yield memory representations of a contextual fear response that are differentially sensitive to HPC lesions. Thus, allowing normal animals adequate pre-exposure followed by delivery of a few, appropriately distributed shocks will lead to a contextual representation that is dependent on the HPC shortly after acquisition. Increasing the number of shocks or delivering them under massed conditions may restrict the representation to one or two salient elements rather than the entire contextual configuration. Such a representation may be weakly dependent on the HPC, or not dependent on it at all.

Memory representations that are not dependent on the HPC during or shortly after acquisition are not likely to be HPC-dependent when memory is tested at longer delays. Even if the representations are dependent on the HPC at acquisition, there is no guarantee that they will remain that way at longer delays. Some memory representations are altered with time so that they become less contextually rich and specific and, thereby, become independent of the HPC (e.g., Wiltgen et al., 2010; Winocur et al., 2007), whereas others retain their specificity and HPC-dependence (e.g., Wang et al., 2009; Wiltgen et al., 2010). We believe that these considerations likely account for some of the variable findings on gradients in remote memory. Because there is no formula, nor even reliable guidelines, for ensuring that one or the other kind of memory is formed, it is important to ascertain what the nature of the memory representation is that supports the contextual fear response. One way to do this is to determine whether the response is context specific at the time of test, and whether the specificity is dependent on overall context, rather than on some local element which the rat may use to distinguish one context from the other. The following section picks up on this notion and reviews an experimental approach that has proven useful in shedding light on this issue.

5. Context manipulation and memory

There is no disagreement amongst the various theories over the effects of HPC lesions on recently acquired premorbid memories – all predict that such memories are extremely vulnerable. The disagreement arises over the fate of remote memories – SCT holds that they are spared; Overshadowing Theory maintains that they are lost; MT-T Theory argues that they can be lost or spared, depending on the test, the original representation, and whether sufficient time and experience has elapsed to allow the transformation process to be completed.

An important observation that bears directly on this issue is that memories that are retrieved shortly after learning differ in terms of their contextual richness from those recalled from the remote past. Riccio and colleagues (Riccio & Ebner, 1981; Riccio, Richardson, & Ebner, 1984) established that certain Pavlovian fear conditioned responses are context-specific shortly after conditioning but, at longer intervals, the response generalizes to other contexts. The same effect has been demonstrated in contextual fear conditioning (Biedenkapp & Rudy, 2007; Fanselow, 1980; Wiltgen & Silva, 2007; Winocur et al., 2007; see also Alvares Lde et al., 2012; Wang et al., 2009). That is, when tested within 24 h of training in the conditioning chamber (Context A), normal rodents exhibited the expected freezing response, but not when tested in an unfamiliar chamber (Context B). However, when tested several days later, the animals exhibited the fear response in both contexts.[8]

This effect, as demonstrated by Winocur et al. (2007, 2009), is represented graphically in Fig. 1 (Top). Rats with HPC lesions were also included in this experiment and, significantly, as can be seen in Fig. 1, these animals were unresponsive to changes in context. Winocur et al. (2007) reported the same results in the socially-acquired food preference task, which is also associated with TGRA in HPC-damaged rats (Winocur, 1990).

Biedenkapp and Rudy (2007) suggested that the generalized response at long delays reflected weakening of the originally learned fear response. Indeed, some weakening may have occurred through

[8] The same effects were seen in normal animals on the food-preference task. An interesting question is whether this pattern would also be observed if the food flavours were varied at test along a similarity dimension. MT-T Theory would predict good discrimination between familiar and new flavours at short intervals (context specificity) but generalized preferences at long delays. A generalized flavour preference at long delays might well combine a transformed memory for flavour ***and*** a transformed memory for the test context. Context-dependent memory would discourage selection of the target food in the same environment where it may not be biologically adaptive to persist with that response, and context-independent memory, which evokes a less precise representation of the environment, would favour selection of a previously experienced and safe food. At long delays, normal rats would show greater preference for the target food in a different environment (where the cues evoke memory for the learned preference without competing influences from context-dependent memory), than in the training environment (where the memories are in conflict) which, in fact, is what we found (Winocur et al., 2007).

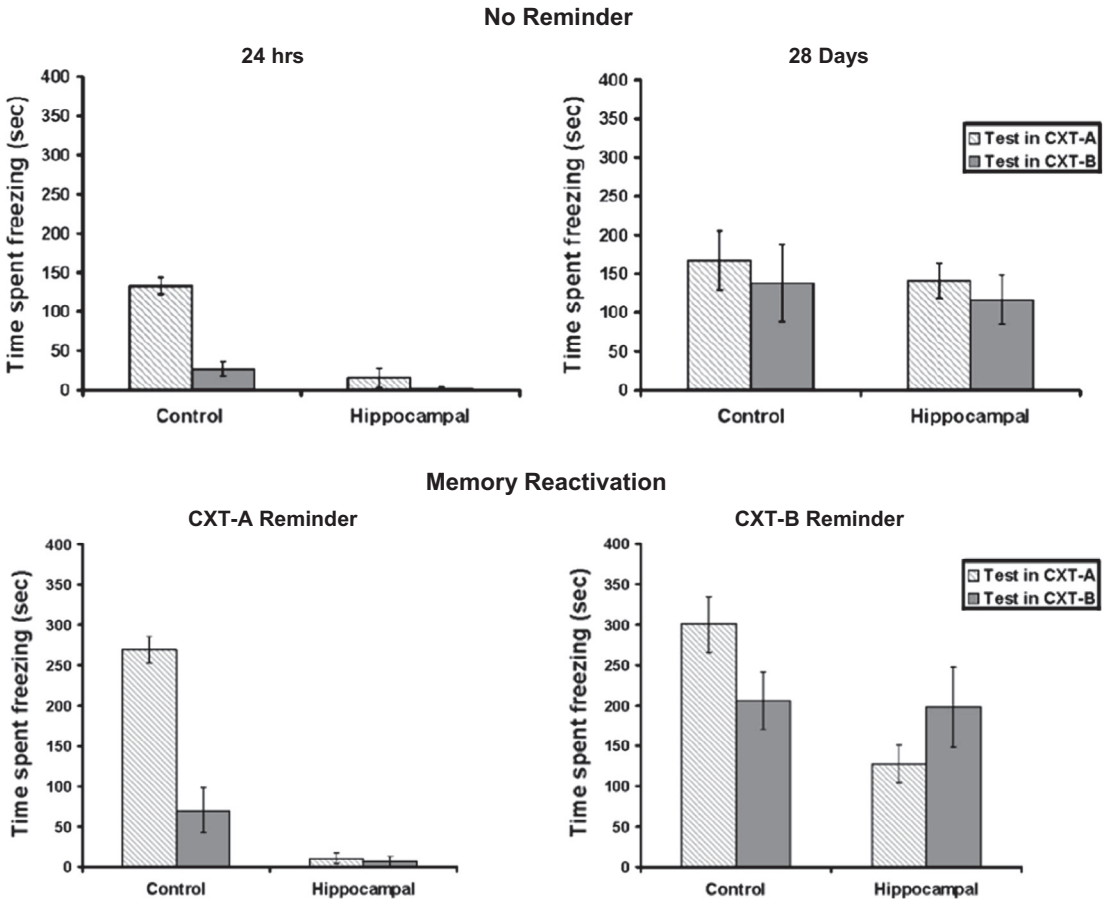

Fig. 1. (Top) Contextual fear memory tested in training (CXT A) or unfamiliar (CXT B) contexts at training – surgery intervals of 24 h. or 28 days. At 24 h., controls exhibited context-specificity, while rats with hippocampal lesions showed no memory of the fear response. At 28 days, both groups exhibited strong memory in both contexts. (Bottom) Memory Reactivation. Contextual fear memory was tested after CXT A or CXT B was provided as a reminder 24 h before surgery, 28 days after conditioning in CXT A. CXT A reactivated the context-specific memory, which was eliminated by hippocampal lesions. CXT B activated a non-specific memory of the fear response, which resulted in generalized freezing in lesioned and control groups. Error bars represent ± SEM. (Adapted with permission from Winocur et al., 2009.)

forgetting, but in our view, the crucial factor is that recent and remote memories have different characteristics apart from strength (Hardt, Nader, & Nadel, 2013). Winocur et al. (2009) trained normal rats on a contextual fear conditioning task in Context A and 28 days later, following procedures common to reconsolidation paradigms (Nader & Hardt, 2009) reminded them of the training experience by placing them for a brief period in either Context A or a different context (B). Immediately after the reminder, rats received either HPC lesions or sham surgery and, on recovery, were tested in either Context A or Context B (Fig. 1Bottom). Consistent with predictions from MT-T Theory, the effect of the Context A reminder on control rats was to restore the context-specificity of the fear response, which was lost during the delay. The Context B reminder did not evoke context specificity in the controls but, rather, a generalized freezing response. Following the Context A reminder, HPC lesions disrupted memory for the fear response when rats were tested in Context A. Interestingly, rats reminded in Context A, were also impaired when tested in Context B following HPC lesions. The latter result was unexpected from the MT-T viewpoint and could reflect forgetting-induced susceptibility to the effects of HPC lesions. It could also represent an inhibitory or competitive effect resulting from the dominance of the reactivated context-specific, HPC-dependent memory. Under such inhibitory control, the generalized (schematic) memory, along with the context-specific memory may have been disrupted by HPC lesions. This result may speak to the complexity of the relationship between context-specific and schematic memories, as well as to the impact of forgetting and inhibitory processes on this relationship (see also Dudai, 2012; Dudai & Eisenberg, 2004, for similar arguments regarding reconsolidation and extinction).[9]

MT-T Theory best accounts for at least one important aspect of Winocur et al.'s (2009) results. In contrast to the effect of HPC lesions on a Context A-reactivated memory, such lesions had no effect on performance following a Context B reminder. As can be seen in Fig. 1 (Bottom), the HPC group retrieved the fear response when tested in Context A or Context B. According to this account, the effect of the Context B reminder was to reactivate the schematic version of the contextual fear memory, which could be accessed when tested in either context. This memory, which is represented outside the HPC, would not be affected by lesions to this structure.

[9] The complex relationship between HPC and neocortical representations of recent and remote memories is underscored by Goshen et al.'s (2011) study using optogenetic inhibition to disrupt the HPC temporarily during tests of contextual fear memory. They observed that delivering a brief pulse of light to optogenetically inhibit excitatory neurons in eNpHR3.1 mice rapidly reduced spiking frequency in CA1 excitatory neurons and eliminated the typical fear response, even at remote intervals, while the light was on; the response returned to control levels as soon as the light was turned off. This finding suggests that the HPC mediated the fear response at remote intervals. If the light remained on for an extended period (half hour), the effect now mimicked that which is typically observed after HPC lesions, and the mouse froze, as expected. These observations suggest that the HPC-mediated memory is the mouse's default option, even at remote intervals. If the HPC is incapacitated for a long interval, as is the case in lesion studies, then the mouse resorts to the neocortically-represented memory. The mechanisms that determine this shift are unknown.

The results of the Winocur et al. (2009) reactivation experiment pose problems for the alternative theories being considered here. SCT makes no provision for the reactivation or reconsolidation effects created by a reminder following a long delay. To do so would require the assumption that the contextual fear memory, after it has become consolidated in neocortical structures, somehow returns to the HPC. As noted above, there was some support for the Overshadowing account in the behaviour of the Context A-reminded HPC group that was tested in Context B. However, by this view, when the HPC system is recruited to mediate new learning, other neural systems are suppressed and do not participate in the learning. Thus, HPC lesions should destroy the representation of the memory, leaving no possibility for its reactivation. Accordingly, the freezing displayed by the Context B-reminded HPC group in Contexts A and B would not be predicted.

In related work, Wiltgen and colleagues (Tayler et al., 2011; Wiltgen, Wood, & Levy, 2011) examined the effects of blocking N-methyl-D-asparate receptor (NMDAR) activity in the HPC on learning and remembering a contextual fear response in different contexts. Their procedure was to treat mice with an NMDAR antagonist or saline prior to fear conditioning in Context A. Several days later, mice that had been treated previously with an antagonist now received saline treatment, and vice versa. All the mice then underwent fear conditioning in Context B.

As expected, antagonist-treated mice were impaired in learning the fear response in Context A. The interesting finding was that the mice treated first with saline and trained in Context A, had no trouble later acquiring the fear response in Context B despite having been treated with an NMDAR antagonist (see Hardt, Wang, & Nader, 2009; Sanders & Fanselow, 2003, for similar findings). Wiltgen and colleagues suggested that the second response acquired in Context B was also context-specific but mediated by different mechanisms that did not depend on NMDAR activity in the hippocampus. An alternate interpretation, consistent with MT-T Theory, is that a schematic version of the contextual fear memory, which is not affected by HPC disruption, formed between the two training sessions. The finding is also consistent with Overshadowing Theory, which would argue that fear conditioning by the antagonist group in Context B was mediated by extra-HPC structures. However, if this were true, one would also expect the antagonist-treated mice to have acquired a contextual fear response when trained in Context A.

6. Within-group studies of retrograde memory

Almost all studies of the effects of HPC lesions on retrograde memory have employed between-group designs in which recent memory and remote memory are tested in different groups of animals. A few have employed more sensitive within-group designs in which animals are administered both recent and remote memory tests. Despite the limited number of such studies, the results bear directly on the issues raised here and are informative.

In one of the first within-group studies (Cho, Kesner, & Brodale, 1995), normal rats were trained successively on two different spatial discrimination problems and, 24 h after the second task, sustained lesions to the HPC or entorhinal cortex. The interval between the end of training on the first task and surgery was relatively short (3–5 days), although it was sufficient to reveal TGRA and preserved remote memory in the group with entorhinal cortex lesions. Consistent with findings from between-group studies, the HPC group exhibited amnesia for both learned responses. This study should be repeated with longer training-surgery intervals but the results are in line with most studies of retrograde spatial memory following HPC lesions. They are also consistent with the MT-T and Overshadowing theoretical positions.

Anagnostaras et al. (1999) used a within-group design to test the effects of HPC lesions on retrograde memory of tone-signaled and contextual fear responses. Normal rats received 10 tone (2 Hz) – shock pairings in Context A. Fifty days later they received the same training procedure with a different tone (8 Hz) in Context B, followed by HPC or sham surgery. Following recovery, contextual fear was tested in Context A and, 24 h later, in Context B. Memory for signaled fear was tested by presenting each tone in a different context (Context C).

With respect to contextual fear, there was no difference between groups on the remote memory test (Context A) but the HPC Group froze significantly less than the control group in the recent memory test (Context B). There was no effect of lesion in either the recent or remote memory test of tone-conditioned fear. These results, which would not have been predicted by Overshadowing Theory, were interpreted as support for SCT.

On the surface, the results appear incompatible with MT-T Theory, which maintains that the 50-day interval between the fear conditioning trials should have been sufficient to enable schematization of the fear response acquired in Context A, and generalization to similar contexts. On that argument, the schematized memory should survive HPC lesions so that, in post-operative testing, the HPC group would be expected to exhibit substantial freezing in both Context A or Context B. This was not the case, but close examination of the data reveals that the outcome can be explained within the framework of MT-T Theory. Fig. 3A of their paper (reproduced here in Fig. 2, left panel) shows that, over the 8-min remote memory test in Context A, rats with HPC lesions exhibited considerable freezing at the beginning of the test (70% freezing score) that decreased to about 50% by the 8th minute, indicating an extinction process. According to MT-T Theory, freezing by the HPC group would be an expression of their schematized memory of the fear response. Fig. 3B of their paper (reproduced here in Fig. 2, right panel) shows that the next day, when recent memory was tested in Context B, the HPC group initially continued to freeze at the 50% rate and then declined rapidly to less than 15% freezing by the 8th minute of the test. This pattern can be interpreted as indicating that the HPC group retrieved a transformed schematized version of the fear response in both contexts, which progressively extinguished over two days of non-reinforced testing.

The control rats also may have relied on schematic memory to mediate fear responses but this is counter-indicated by their overall pattern of behaviour, which was different from that of the HPC group. In Context A, the control group, like the HPC group, initially responded at a high level and gradually declined to a 50% response rate. However, unlike the HPC group, when subsequently tested in Context B, the controls rebounded and, as in Context A, maintained a high level of freezing for several minutes before declining to the 50% level. It appears that, with the HPC intact, the controls remembered the specific conditioning experiences associated with Contexts A and B, and that with all the respective training cues present at each test, the corresponding context-specific memories were recruited.

A recently completed study in our lab employed a within-group experimental design to conduct a strong test of MT-T Theory (Winocur et al., 2013). As described above, a central premise of this theory is that, on tests of retrograde memory, HPC lesions can result in graded or non-graded RA, depending on the type of memory assessed. It follows that it should be possible to demonstrate both patterns of amnesia in the same individual simply by varying the test. In fact, this has been reported in the human literature (Barr, Goldberg, Wasserstein, & Novelly, 1990; Cermak & O'Connor, 1983; Rosenbaum et al., 2008; Steinvorth et al., 2005). When administered tests of autobiographical, context-dependent memory, medial temporal lobe-amnesic patients, including HM, exhibited non-graded RA extending back decades in some cases. The

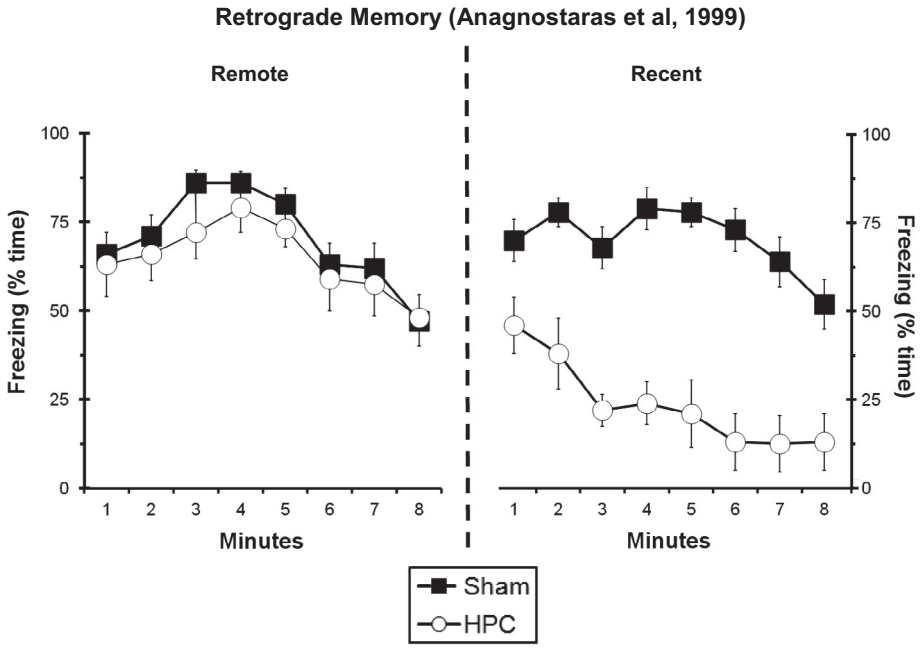

Fig. 2. Retrograde amnesia in a within-subjects design. (Left) Hippocampal and control groups exhibit equivalent memory for a contextual fear response that was conditioned 50 days before surgery. (Right) The hippocampal group exhibited less memory for a contextual fear response that was conditioned in a different context 24 before surgery. Error bars represent ±SEM. (Adapted with permission from Anagnostaras et al., 1999.)

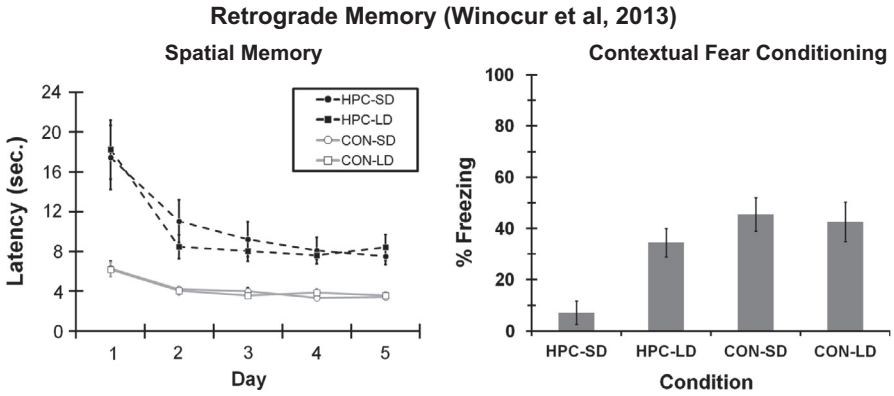

Fig. 3. Retrograde memory tested in the same hippocampal and control groups following short (24 h) and long (28 days) training – surgery intervals. (Left) Spatial Memory. Hippocampal groups were impaired at both delays. (Right) Contextual fear rmemory. The hippocampal group was impaired at the short delay, but not the long delay. Error bars represent ± SEM. Abbreviations: HPC – Hippocampal; CON– Control; SD – Short Delay; LD – Long Delay. (Adapted with permission from Winocur et al., 2013.)

same patients displayed TGRA when administered tests of semantic or schematic memory.

We sought to determine if the same intra-individual dissociation can be demonstrated in an animal model where conditions can be controlled more rigorously than in clinical studies. In this experiment, rats completed training on the spatial Morris water maze test and received contextual fear conditioning before undergoing HPC or sham surgery, 24 h or 28 days later. This type of spatial memory test, which is dependent on access to the rich contextual associations that supported the original learning and always requires the HPC, is considered analogous to tests of context-specific, episodic memories in humans (Winocur et al., 2005). By comparison, a contextual fear response is thought to be context-specific for a short while after training but, with time, becomes less tied to the training context and increasingly independent of the HPC. Consistent with this analysis, the spatial memory test reliably yields RA regardless of when pre-operative training took place. As discussed above, following our procedures, rats with HPC lesions consistently display TGRA on tests of contextual fear conditioning. After recovery from surgery, animals in the two training-surgery interval conditions were tested on both tasks.

As expected, on the recent memory tests, rats with HPC lesions were impaired on both tasks (see Fig. 3). However, on the remote memory tests, the HPC group was impaired only on the spatial memory task.[10] The results are not consistent with either SCT, which

[10] It has been suggested that the extended RA observed in HPC-damaged animals on spatial memory tasks is a failure in navigation or on-line spatial processing, rather than loss of the specific memory (Clark et al., 2005a, 2005b). This argument is problematic for several reasons (see Winocur et al., 2013) but a major difficulty relates to the finding that, with sufficient pre-operative experience, rats (Winocur et al., 2005, 2010) and humans (Rosenbaum et al., 2000; Teng & Squire, 1999) can form schematic representations of their environment, which will support efficient spatial memory following HPC lesions. Spatial memories based on this type of representation, like those based on hippocampal cognitive maps, have in common the feature that they both require on-line spatial processing, and it is unclear why HPC lesions would impair such processing in one case but not the other.

predicts TGRA in all cases, or Overshadowing Theory, which predicts non-graded RA in all cases, but they confirm crucial predictions of MT-T Theory.

The three studies that employed a within-group design to test the effects of HPC lesions on retrograde memory provide varying support for the theoretical positions considered here. SCT received support from the Anagnostaras et al. (1999) study and Overshadowing Theory was endorsed by the Cho et al. (1995) study. However, both sets of results can be explained by MT-T Theory which, in addition, is the only theory to predict the outcome of the Winocur et al. (2013) study. Thus, all the results are consistent with MT-T Theory and, as such, provide important support for this theoretical account.

7. Summary, conclusions, and future directions

In this review we continue the debate over which of three current theories best explains the role of the HPC in recent and remote memory – SCT (Squire & Wixted, 2011), Overshadowing Theory (Sutherland et al., 2010), and MT-T Theory (Winocur et al., 2010). SCT and Overshadowing Theory share the idea that the nature of memory representations does not change fundamentally over time. For SCT, what changes is the neural substrate that mediates those memories, whereas for Overshadowing Theory, different types of memory are always mediated by the neural systems that participated in their formation. By contrast, MT-T Theory holds that memory representations are mutable, transforming over time and experience, from detailed memories that are context-specific and mediated initially by the HPC, to more schematic versions mediated by extra-HPC (neocortical) structures.

It should be noted that memory transformation is likely not a linear process, and that plasticity in extra-HPC regions (including, for example, the anterior cingulate cortex, ACC) starts to interact with the HPC shortly after memory acquisition to mediate the formation of the remote memory trace. In support of this view, several studies have shown that, following memory acquisition, the HPC drives changes in dendritic excitatory spine growth/density in the ACC (Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004; Restivo, Vetere, Bontempi, & Ammassari-Teule, 2009; Vetere et al., 2011). As well, Restivo et al. (2009) found that HPC lesions made one day after contextual fear conditioning impaired context memory shortly following lesioning and prevented increases in dendritic spine density in the ACC. In contrast, HPC lesions made several weeks after conditioning did not affect spine density in the ACC, or impair freezing during remote memory testing (see also Vetere et al., 2011).

We view memory consolidation as a dynamic process, where a fear memory not only undergoes a process of reorganization and transformation at the systems level, but can also revert to a previous vulnerable state where it is again susceptible to interference or disruption (Nader, Schafe, & LeDoux, 2000; Dudai, 2004; Nader & Hardt, 2009; see Dudai, 2012 for review). Re-exposure to precise contextual cues present during memory acquisition can return a remote schematic/generalized HPC-independent memory to a context-specific HPC-mediated memory (Debiec, LeDoux, & Nader, 2002; Sekeres et al., 2012; Wiltgen & Silva, 2007; Winocur et al., 2007; interestingly, protein-synthesis inhibition in the ACC can also disrupt reconsolidation of both recent and remote context memory following a context reminder (Einarsson & Nader, 2012). Consistent with MT-T, the idea that appropriate 'reminders' can return a schematic memory to a context-specific memory that is susceptible to HPC interference suggests that the two types of memories, detailed context-specific memories and gist-like schematic memories, can co-exist and the demands at retrieval will influence which version of the memory will be expressed.

In reviewing the evidence, we focused on the animal literature and three types of tasks which have been used most often in this research – spatial memory, socially-transmitted food preference, and contextual fear conditioning. With respect to spatial memory and food preference, the results, taken as a whole, have been consistent and most in line with MT-T Theory. The extensive non-graded RA observed on spatial tasks which always depend on maintaining rich, context-specific representations, are incompatible with SCT; the TGRA consistently seen on the food preference task, which entails a change from a context-specific to a schematic representation, is incompatible with Overshadowing Theory.

In contrast, studies of contextual fear conditioning pose a problem for interpretation because there are numerous discrepancies in the results. Some investigators have reported that HPC lesions produce TGRA (e.g., Corcoran et al., 2011; Kim & Fanselow, 1992; Winocur et al., 2009, 2013), while others report non-graded RA (e.g., Lehmann et al., 2007, 2009; Sutherland, O'Brien, & Lehmann, 2008). A similar inconsistency exists with respect to the effects of HPC lesions on the acquisition of a contextual fear response – some studies found normal learning (e.g., Frankland et al., 1998; Maren et al., 1997), whereas others reveal significant impairment (Maren & Fanselow, 1997; Philips & LeDoux, 1992, 1994; Winocur et al., 2007). Our review of the contextual fear literature suggests that a number of factors, including the complexity of the conditioning environment, amount of pre-exposure to the conditioning chamber, and the number and distribution of foot-shocks, may contribute to the inconsistent results. More work needs to be done to determine the relative importance of the various factors and how they interact with each other. Nevertheless, our review leads us to conclude that when experimental conditions are conducive to the formation of a detailed and well-integrated HPC-dependent contextual fear response, memories often will transform into a schematic version that is resistant to the effects of HPC damage. This evidence, along with other research strategies that involve, for example, the manipulation of contextual cues and within-groups experimental designs provide important support for the MT-T theoretical position.

A number of outstanding issues around MT-T need to be resolved and foremost among them relates to the mechanisms underlying memory transformation. One possible mechanism involves decay. By decay, we refer not to the diminished strength of a memory but some loss of attributes that alter the representation from one that is detailed and well-integrated, to one that is impoverished, schematic, and less cohesive. Following this reasoning, over time and experience, the memory's sensitivity to perceptual aspects of the environment would be lost or degraded, as would memory for the configural relations among the features of the environment.

The influence of existing schemas, characterized as cognitive frameworks within which new information can be organized, can also influence the memory transformation process. The more easily a new memory can be integrated into an existing schema, the more likely that memory will rely on the schematic representation or gist that the schema affords, rather than the specific, contextual aspects which make the memory unique. In the animal literature, possible support for this notion comes from Tse et al. (2007), who showed that new HPC-mediated memories can be acquired quickly when supported by a pre-existing schema, but become rapidly independent of the HPC. In this case, the ventro-medial prefrontal cortex may play a special role in promoting schematic memories, as suggested by observations of this structure's role in forming and using schemas, as well as in supporting remote memories, in rats (Bontempi, Laurent-Demir, Destrade, & Jaffard, 1999; Frankland & Bontempi, 2005) and humans (van Kesteren, Rijpkema, Ruiter, & Fernandez, 2010).

A third mechanism that can also be aligned with the transformation view relates to the disruptive effects of interference. It is possible the formation of a new memory competes with and replaces an existing memory, so that the contextual details of the latter cannot be expressed and only its gist is retained. It is also possible that an interfering memory can be incorporated into an existing memory, forming a new memory that has characteristics of both (see Hupbach, Hardt, Gomez, & Nadel, 2008).

It is likely that each of these alternatives, and probably others, influence and drive memory transformation. Some of these mechanisms, such as decay, seem passive (although the 'active decay' hypothesis proposes that memories can be actively removed/transformed on the basis of relevance and recency via mechanisms that include pruning of weakly potentiated synapses in the HPC and increasing AMPAR internalization; see Hardt et al., 2013 for review), but others, such as assimilation to existing schemas may have a more active component. Research in this areas is just beginning but all indications are that it will proliferate and reinforce the view, which is at the heart of MT-T Theory, that memory is a dynamic, interactive process.

Acknowledgments

The preparation of this paper, as well as some of the research reported therein was supported by a grant to GW and MM by the Canadian Institutes for Health Research (Grant No.: MGP 6694). Other research by the authors reported in this paper was supported by grants from the Natural Sciences and Engineering Research Council to GW and MM. MS was supported by a post-doctoral fellowship from the Canadian Institutes for Health Research. The authors gratefully acknowledge the support of Mr. Nick Hoang in preparing the manuscript.

References

Alvares Lde, O., Einarsson, E. O., Santana, F., Crestani, A. P., Haubrich, J., Cassini, L. F., et al. (2012). Periodically reactivated context memory retains its precision and dependence on the hippocampus. *Hippocampus, 22*, 1092–1095.

Alvarez, P., Wendelken, L., & Eichenbaum, H. (2002). Hippocampal formation lesions impair performance in an odor–odor association task independently of spatial context. *Neurobiology of Learning and Memory, 78*, 470–476.

Anagnostaras, S. G., Maren, S., & Fanselow, M. S. (1999). Temporally graded retrograde amnesia of contextual fear after hippocampal damage in rats: Within-subjects examination. *Journal of Neuroscience, 19*, 1106–1114.

Athos, J., Impey, S., Pineda, W., Chen, X., & Storm, D. R. (2002). Hippocampal CRE-mediated gene expression is required for contextual memory formation. *Nature Neuroscience, 5*, 1119–1120.

Barr, W. B., Goldberg, E., Wasserstein, J., & Novelly, R. A. (1990). Retrograde amnesia following unilateral temporal lobectomy. *Neuropsychologia, 28*, 243–255.

Bast, T., Zhang, W. N., & Feldon, J. (2001). The ventral hippocampus and fear conditioning in rats. Different anterograde amnesias of fear after tetrodotoxin inactivation and infusion of the GABA(A) agonist muscimol. *Experimental Brain Research, 139*, 39–52.

Bast, T., Zhang, W. N., & Feldon, J. (2003). Dorsal hippocampus and classical fear conditioning to tone and context in rats: Effects of local NMDA-receptor blockade and stimulation. *Hippocampus, 13*, 657–675.

Biedenkapp, J. C., & Rudy, J. W. (2007). Context preexposure prevents forgetting of a contextual fear memory: Implication for regional changes in brain activation patterns associated with recent and remote memory tests. *Learning and Memory, 14*, 200–203.

Bontempi, B., Laurent-Demir, C., Destrade, C., & Jaffard, R. (1999). Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature, 400*, 671–675.

Broadbent, N. J., Squire, L. R., & Clark, R. E. (2007). Rats depend on habit memory for discrimination learning and retention. *Learning and Memory, 14*, 145–151.

Bunsey, M., & Eichenbaum, H. (1995). Selective damage to the hippocampal region blocks long-term retention of a natural and nonspatial stimulus–stimulus association. *Hippocampus, 5*, 546–556.

Burton, S., Murphy, D., Qureshi, U., Sutton, P., & O'Keefe, J. (2000). Combined lesions of hippocampus and subiculum do not produce deficits in a nonspatial social olfactory memory task. *Journal of Neuroscience, 20*, 5468–5475.

Cermak, L. S., & O'Connor, M. (1983). The anterograde and retrograde retrieval ability of a patient with amnesia due to encephalitis. *Neuropsychologia, 21*, 213–234.

Cho, Y. H., Friedman, E., & Silva, A. J. (1999). Ibotenate lesions of the hippocampus impair spatial learning but not contextual fear conditioning in mice. *Behavioral Brain Research, 98*, 77–87.

Cho, Y. H., Kesner, B. P., & Brodale, S. (1995). Retrograde and anterograde amnesia for spatial discrimination in rats: Role of hippocampus, entorhinal cortex, and parietal cortex. *Psychobiology, 23*, 185–194.

Clark, R. E., Broadbent, N. J., & Squire, L. R. (2005a). Hippocampus and remote spatial memory in rats. *Hippocampus, 15*, 260–272.

Clark, R. E., Broadbent, N. J., & Squire, L. R. (2005b). Impaired remote spatial memory after hippocampal lesions despite extensive training beginning early in life. *Hippocampus, 15*, 340–346.

Clark, R. E., Broadbent, N. J., Zola, S. M., & Squire, L. R. (2002). Anterograde amnesia and temporally graded retrograde amnesia for a nonspatial memory task after lesions of hippocampus and subiculum. *Journal of Neuroscience, 22*, 4663–4669.

Corcoran, K. A., Donnan, M. D., Tronson, N. C., Guzman, Y. F., Gao, C., Jovasevic, V., et al. (2011). NMDA receptors in retrosplenial cortex are necessary for retrieval of recent and remote context fear memory. *Journal of Neuroscience, 31*, 11655–11659.

Czerniawski, J., Ree, F., Chia, C., & Otto, T. (2012). Dorsal versus ventral hippocampal contributions to trace and contextual conditioning: Differential effects of regionally selective NMDA receptor antagonism on acquisition and expression. *Hippocampus, 22*, 1528–1539.

Czerniawski, J., Ree, F., Chia, C., Ramamoorthi, K., Kumata, Y., & Otto, T. A. (2011). The importance of having Arc: Expression of the immediate-early gene Arc is required for hippocampus-dependent fear conditioning and blocked by NMDA receptor antagonism. *Journal of Neuroscience, 31*, 11200–11207.

Debiec, J., LeDoux, J. E., & Nader, K. (2002). Cellular and systems reconsolidation in the hippocampus. *Neuron, 36*, 527–538.

Dudai, Y. (2012). The restless engram: Consolidations never end. *Annual Review of Neuroscience, 35*, 227–247.

Dudai, Y., & Eisenberg, M. (2004). Rites of passage of the engram: Reconsolidation and the lingering consolidation hypothesis. *Neuron, 44*, 93–100.

Eichenbaum, H., & Cohen, N. J. (2001). Relational memory processing (declarative versus procedureal memory). In H. Eichenbaum & N. J. Cohen (Eds.), *From conditioning to conscious recollection* (pp. 179–182). New York: Oxford University Press.

Einarsson, E. O., & Nader, K. (2012). Involvement of the anterior cingulate cortex in formation, consolidation, and reconsolidation of recent and remote contextual fear memory. *Learning and Memory, 19*, 449–452.

Esclassan, F., Coutureau, E., Di Scala, G., & Marchand, A. R. (2009). Differential contribution of dorsal and ventral hippocampus to trace and delay fear conditioning. *Hippocampus, 19*, 33–44.

Fanselow, M. S. (1980). Conditioned and unconditional components of post-shock freezing. *Pavlovian Journal of Biological Science, 15*, 177–182.

Fanselow, M. S. (1990). Factors governing one-trial contextual conditioning. *Animal Learning and Behavior, 18*, 264–270.

Fanselow, M. S. (2010). From contextual fear to a dynamic view of memory systems. *Trends in Cognitive Science, 14*, 7–15.

Fleischmann, A., Hvalby, O., Jensen, V., Strekalova, T., Zacher, C., Layer, L. E., et al. (2003). Impaired long-term memory and NR2A-type NMDA receptor-dependent synaptic plasticity in mice lacking c-Fos in the CNS. *Journal of Neuroscience, 23*, 9116–9122.

Frankland, P. W., & Bontempi, B. (2005). The organization of recent and remote memories. *Nature Reviews Neuroscience, 6*, 119–130.

Frankland, P. W., Bontempi, B., Talton, L. E., Kaczmarek, L., & Silva, A. J. (2004). The involvement of the anterior cingulate cortex in remote contextual fear memory. *Science, 304*, 881–883.

Frankland, P. W., Cestari, V., Filipkowski, R. K., McDonald, R. J., & Silva, A. J. (1998). The dorsal hippocampus is essential for context discrimination but not for contextual conditioning. *Behavioral Neuroscience, 112*, 863–874.

Frankland, P. W., Ding, H. K., Takahashi, E., Suzuki, A., Kida, S., & Silva, A. J. (2006). Stability of recent and remote contextual fear memory. *Learning and Memory, 13*, 451–457.

Frankland, P. W., Josselyn, S. A., Anagnostaras, S. G., Kogan, J. H., Takahashi, E., & Silva, A. J. (2004). Consolidation of CS and US representations in associative fear conditioning. *Hippocampus, 14*, 557–569.

Galef, B. G., Kennett, D. J., & Stein, M. (1985). Demonstrator influence on observer diet preference: Effects of simple exposure and the presence of a demonstrator. *Animal Learning and Behavior, 13*, 25–30.

Gaskin, S., Tremblay, A., & Mumby, D. G. (2003). Retrograde and anterograde object recognition in rats with hippocampal lesions. *Hippocampus, 13*, 962–969.

Gerlai, R. (1998). Contextual learning and cue association in fear conditioning in mice: A strain comparison and a lesion study. *Behavioral Brain Research, 95*, 191–203.

Gisquet-Verrier, P., Dutrieux, G., Richer, P., & Doyere, V. (1999). Effects of lesions to the hippocampus on contextual fear: Evidence for a disruption of freezing and avoidance behavior but not context conditioning. *Behavioral Neuroscience, 113*, 507–522.

Gluck, M. A., & Myers, C. E. (1993). Hippocampal mediation of stimulus representation: A computational theory. *Hippocampus, 3*, 491–516.

Good, M., & Honey, R. C. (1991). Conditioning and contextual retrieval in hippocampal rats. *Behavioral Neuroscience, 105*, 499–509.

Goshen, I., Brodsky, M., Prakash, R., Wallace, J., Gradinaru, V., Ramakrishnan, C., et al. (2011). Dynamics of retrieval strategies for remote memories. *Cell, 147*, 678–689.

Gulbrandsen, T. L., Sparks, F. T., & Sutherland, R. J. (2013). Interfering with post-learning hippocampal activity does not affect long-term consolidation of a context fear memory outside the hippocampus. *Behavioral Brain Research, 240*, 103–109.

Hardt, O., Nader, K., & Nadel, L. (2013). Decay happens: The role of active forgetting in memory. *Trends in Cognitive Science, 17*, 111–120.

Hardt, O., Wang, S. H., & Nader, Kl. (2009). Storage or retrieval deficit: The yin and yang of amnesia. *Learning and Memory, 16*, 224–230.

Hernandez-Rabaza, V., Llorens-Martin, M., Velazquez-Sanchez, C., Ferraqud, A., Arcusa, A., Gumus, H. G., et al. (2009). Inhibition of adult hippocampal neurogenesis disrupts contextual learning but spares spatial working memory, long-term conditional rule retention and spatial reversal. *Neuroscience, 159*, 59–68.

Hirsh, R. (1974). The hippocampus and contextual retrieval of information from memory: A theory. *Behavioral Biology, 12*, 421–444.

Hirsh, R. (1980). The hippocampus, conditional operations, and cognition. *Physiological Psychology, 8*, 175–182.

Hirsh, R., Leber, B., & Gillamn, K. (1978). Fornix fibers and motivational states as controllers of behavior: A study stimulated by the contextual retrieval theory. *Behavioral Biology, 22*, 463–478.

Hupbach, A., Hardt, O., Gomez, R., & Nadel, L. (2008). The dynamics of memory: Context-dependent updating. *Learning and Memory, 15*, 574–579.

Kathirvelu, B., East, B. S., Smith, C. A., & Colombo, P. J. (2013). Lentivirus-mediated chronic expression of dominant-negative CREB in the dorsal hippocampus impairs memory for place learning and contextual fear conditioning. *Neurobiology of Learning and Memory, 99*, 10–16.

Kensinger, E. A., Piguet, O., Krendl, A. C., & Corkin, S. (2005). Memory for contextual details: Effects of emotion and aging. *Psychology and Aging, 20*, 241–250.

Kida, S., Josselyn, S. A., Pena de Ortiz, S., Kogan, J. H., Chevere, I., Masushige, S., et al. (2002). CREB required for the stability of new and reactivated fear memories. *Nature Neuroscience, 5*, 348–355.

Kiernan, M. J., & Westbrook, R. F. (1993). Effects of exposure to a to-be-shocked environment upon the rat's freezing response: Evidence for facilitation, latent inhibition, and perceptual learning. *Quarterly Journal of Experimental Psychology B, 46*, 271–288.

Kim, J. J., & Fanselow, M. S. (1992). Modality-specific retrograde amnesia of fear. *Science, 256*, 675–677.

Kim, J. J., Rison, R. A., & Fanselow, M. S. (1993). Effects of amygdala, hippocampus, and periaqueductal gray lesions on short- and long-term contextual fear. *Behavioral Neuroscience, 107*, 1093–1098.

Kitamura, T., Saitoh, Y., Takashima, N., Murayama, A., Niibori, Y., Ageta, H., et al. (2009). Adult neurogenesis modulates the hippocampus-dependent period of associative fear memory. *Cell, 139*, 814–827.

Kjelstrup, K. G., Tuvnes, F. A., Steffenach, H. A., Murison, R., Moser, E. I., & Moser, M. B. (2002). Reduced fear expression after lesions of the ventral hippocampus. *Proceedings of the National Academy of Sciences of the United States of America, 99*, 10825–10830.

Lattal, K. M., & Abel, T. (2001). Different requirements for protein synthesis in acquisition and extinction of spatial preferences and context-evoked fear. *Journal of Neuroscience, 21*, 5773–5780.

Lehmann, H., Lacanilao, S., & Sutherland, R. J. (2007). Complete or partial hippocampal damage produces equivalent retrograde amnesia for remote contextual fear memories. *European Journal of Neuroscience, 25*, 1278–1286.

Lehmann, H., Lecluse, V., Houle, A., & Mumby, D. G. (2006). Retrograde amnesia following hippocampal lesions in the shock-probe conditioning test. *Hippocampus, 16*, 379–387.

Lehmann, H., Rourke, B. K., Booker, A., & Gleen, M. J. (2012). Single session contextual fear conditioning remains dependent on the hippocampus despite an increase in the number of context-shock pairings during learning. *Neurobiology of Learning and Memory*. November 7 (Epub ahead of print).

Lehmann, H., Sparks, F. T., Spanswick, S. C., Hadikin, C., McDonald, R. J., & Sutherland, R. J. (2009). Making context memories independent of the hippocampus. *Learning and Memory, 16*, 417–420.

Maren, S. (2001). Neurobiology of Pavlovian fear conditioning. *Annual Review of Neuroscience, 24*, 897–931.

Maren, S., Aharonov, G., & Fanselow, M. S. (1997). Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. *Behavioral Brain Research, 88*, 261–274.

Maren, S., & Fanselow, M. S. (1997). Electrolytic lesions of the fimbria/fornix, dorsal hippocampus, or entorhinal cortex produce anterograde deficits in contextual fear conditioning in rats. *Neurobiology of Learning and Memory, 67*, 142–149.

Marslen-Wilson, W., & Teuber, H.-L. (1975). Memory for remote events in anterograde amnesia: Recognition of public figures from news photographs. *Neuropsychologia, 13*, 353–364.

Martin, S. J., de Hoz, L., & Morris, R. G. (2005). Retrograde amnesia: Neither partial nor complete hippocampal lesions in rats result in preferential sparing of remote spatial memory, even after reminding. *Neuropsychologia, 43*, 609–624.

Matus-Amat, P., Higgins, E. A., Barrientos, R. M., & Rudy, J. W. (2004). The role of the dorsal hippocampus in the acquisition and retrieval of context memory representations. *Journal of Neuroscience, 24*, 2431–2439.

Morris, R. G., Garrud, P., Rawlins, J. N., & Okeefe, J. (1982). Place navigation impaired in rats with hippocampal-lesions. *Nature, 297*, 681–683.

Moscovitch, M. (1992). Memory and working-with-memory: A component process model based on modules and central systems. *Journal of Cognitive Neuroscience, 3*, 257–267.

Moscovitch, M., Rosenbaum, R. S., Gilboa, A., Addis, D. R., Westmacott, R., Grady, C., et al. (2005). Functional neuroanatomy of remote episodic, semantic and spatial memory: A unified account based on multiple trace theory. *Journal of Anatomy, 43*, 35–66.

Moses, S. N., Winocur, G., Ryan, J. D., & Moscovitch, M. (2007). Environmental complexity affects contextual fear conditioning following hippocampal lesions in rats. *Hippocampus, 17*, 333–337.

Nadel, L., & Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Current Opinion in Neurobiology, 7*, 217–227.

Nader, K., & Hardt, O. (2009). A single standard for memory: The case for reconsolidation. *Nature Reviews Neuroscience, 10*, 224–234.

Nader, K., Schafe, G. E., & LeDoux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature, 406*, 722–726.

O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map*. Oxford: Oxford University Press.

Olton, D. S., Becker, J. T., & Handelmann, G. E. (1979). Hippocampus, space, and memory. *Behavioral and Brain Sciences, 2*, 313–365.

Penfield, W., & Milner, B. (1958). Memory deficit produced by bilateral lesions in the hippocampal zone. *AMA Archives of Neurology and Psychiatry, 79*, 475–497.

Phillips, R. G., & LeDoux, J. E. (1992). Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behavioral Neuroscience, 106*, 274–285.

Phillips, R. G., & LeDoux, J. E. (1994). Lesions of the dorsal hippocampal formation interfere with background but not foreground contextual fear conditioning. *Learning and Memory, 1*, 34–44.

Poppenk, J., Evensmoen, H. R., & Moscovitch, M. (2013). Long-axis specialization of the human hippocampus. *Trends in Cognitive Science*.

Poreh, A., Winocur, G., Moscovitch, M., Backon, M., Goshen, E., Ram, Z., et al. (2006). Anterograde and retrograde amnesia in a person with bilateral fornix lesions following removal of a colloid cyst. *Neuropsychologia, 44*, 2241–2248.

Quinn, J. J., Ma, Q. D., Tinsley, M. R., Koch, C., & Fanselow, M. S. (2008). Inverse temporal contributions of the dorsal hippocampus and medial prefrontal cortex to the expression of long-term fear memories. *Learning and Memory, 15*, 368–372.

Quinn, J. J., Wied, H. M., Ma, Q. D., Tinsley, M. R., & Fanselow, M. S. (2008). Dorsal hippocampus involvement in delay fear conditioning depends upon the strength of the tone-footshock association. *Hippocampus, 18*, 640–654.

Ramos, J. M. J. (1998). Retrograde amnesia for spatial information: A dissociation between intra and extramaze cues following hippocampus lesions in rats. *European Journal of Neuroscience, 10*, 3295–3301.

Rampon, C., Tang, Y. P., Goodhouse, J., Shimizu, E., Kyin, M., & Tsien, J. Z. (2000). Enrichment induces structural changes and recovery from nonspatial memory deficits in CA1 NMDAR1-knockout mice. *Nature Neuroscience, 3*, 238–244.

Restivo, L., Vetere, G., Bontempi, B., & Ammassari-Teule, M. (2009). The formation of recent and remote memory is associated with time-dependent formation of dendritic spines in the hippocampus and anterior cingulate cortex. *Journal of Neuroscience, 29*, 8206–8214.

Riccio, D. C., & Ebner, D. (1981). Postacquisition modifications of memory. In N. E. Spear & R. R. Miller (Eds.), *Information processing in animals: Memory mechanisms* (pp. 291–317). Hillsdale, NJ: Erlbaum.

Riccio, D. C., Richardson, R., & Ebner, D. L. (1984). Memory retrieval deficits based upon altered contextual cues: A paradox. *Psychological Bulletin, 96*, 152–165.

Richmond, M. A., Yee, B. K., Pouzet, B., Veenman, L., Rawlins, J. N. P., & Feldon, J. (1999). Dissociating context and space within the hippocampus: Effects of complete, dorsal, and ventral excitotoxic hippocampal lesions on conditioned freezing and spatial learning. *Behavioral Neuroscience, 113*, 1189–1203.

Rosenbaum, R. S., Gilboa, A., Levine, B., Winocur, G., & Moscovitch, M. (2009). Amnesia as an impairment of detail generation and binding: Evidence from personal, fictional, and semantic narratives in K.C. *Neuropsychologia, 47*, 2181–2187.

Rosenbaum, R. S., Moscovitch, M., Foster, J. K., Schnyer, D. M., Gao, F., Kovacevic, N., et al. (2008). Patterns of autobiographical memory loss in medial–temporal lobe amnesic patients. *Journal of Cognitive Neuroscience, 20*, 1490–1506.

Rosenbaum, R. S., Priselac, S., Kohler, S., Black, S. E., Gao, F., Nadel, L., et al. (2000). Remote spatial memory in an amnesic person with extensive bilateral hippocampal lesions. *Nature Neuroscience, 3*, 1044–1048.

Rudy, J. W., Barrientos, R. M., & O'Reilly, R. C. (2002). Hippocampal formation supports conditioning to memory of a context. *Behavioral Neuroscience, 116*, 530–538.

Rudy, J. W., & O'Reilly, R. C. (1999). Contextual fear conditioning, conjunctive representations, pattern completion, and the hippocampus. *Behavioral Neuroscience, 113*, 867–880.

Sanders, M. J., & Fanselow, M. S. (2003). Pre-training prevents context fear conditioning deficits produced by hippocampal NMDA receptor blockade. *Neurobiology of Learning and Memory, 80*, 123–129.

Saxe, M. D., Battaglia, F., Wang, J. W., Malleret, G., David, D. J., Monckton, J. E., et al. (2006). Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. *Proceedings of the National Academy of Sciences of the United States of America, 103*, 17501–17506.

Scoville, W., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry, 20*, 11–21.

Sekeres, M. J., Mercaldo, V., Richards, B., Sargin, D., Mahadevan, V., Woodin, M. A., et al. (2012). Increasing CRTC1 function in the dentate gyrus during memory formation or reactivation increases memory strength without compromising memory quality. *Journal of Neuroscience, 32*, 17857–17868.

Shors, T. J., Townsend, D. A., Zhao, M., Kozorovitskiy, Y., & Gould, E. (2002). Neurogenesis may relate to some but not all types of hippocampal-dependent learning. *Hippocampus, 12*, 578–584.

Sparks, F. T., Lehmann, H., Hernandez, K., & Sutherland, R. S. (2011). Suppression of neurotoxic lesion-induced seizure activity: Evidence for a permanent role for the hippocampus in contextual memory. *PLoS One, 6*, e27426.

Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: A neurobiological perspective. *Current Opinion in Neurobiology, 5*, 169–177.

Squire, L. R., & Wixted, J. T. (2011). The cognitive neuroscience of human memory since H.M. *Annual Review of Neuroscience, 34*, 259–288.

Steinvorth, S., Levine, B., & Corkin, S. (2005). Medial temporal lobe structures are needed to re-experience remote autobiographical memories: Evidence from H.M. and W.R. *Neuropsychologia, 43*, 479–496.

Stiedl, O., Birkenfeld, K., Palve, M., & Spiess, J. (2000). Impairment of conditioned contextual fear of C57BL/6J mice by intracerebral injections of the NMDA receptor antagonist APV. *Behavioral Brain Research, 116*, 157–168.

Sutherland, R. J., & Lehmann, H. (2011). Alternative conceptions of memory consolidation and the role of the hippocampus at the systems level in rodents. *Current Opinions in Neurobiology, 21*, 446–451.

Sutherland, R. J., O'Brien, J., & Lehmann, H. (2008). Absence of systems consolidation of fear memories after dorsal, ventral, or complete hippocampal damage. *Hippocampus, 18*, 710–718.

Sutherland, R. J., & Rudy, J. W. (1989). Configural association theory: The role of the hippocampal formation in learning, memory, amnesia. *Psychobiology, 17*, 129–144.

Sutherland, R. J., Sparks, F. T., & Lehmann, H. (2010). Hippocampus and retrograde amnesia in the rat model: A modest proposal for the situation of systems consolidation. *Neuropsychologia, 48*, 2357–2369.

Sutherland, R. J., Weisend, M. P., Mumby, D., Astur, R. S., Hanlon, F. M., Koerner, A., et al. (2001). Retrograde amnesia after hippocampal damage: Recent vs. remote memories in two tasks. *Hippocampus, 11*, 27–42.

Tayler, K. K., Lowry, E., Tanaka, K., Levy, B., Reijmers, L., Mayford, M., et al. (2011). Characterization of NMDAR-independent learning in the hippocampus. *Frontiers in Behavioral Neuroscience, 5*, 1–12.

Teng, E., & Squire, L. R. (1999). Memory for places learned long ago is intact after hippocampal damage. *Nature, 400*, 675–677.

Teyler, T. J., & DiScenna, P. (1986). The hippocampal memory indexing theory. *Behavioral Neuroscience, 100*, 147–154.

Trivedi, M. A., & Coover, G. D. (2006). Neurotoxic lesions of the dorsal and ventral hippocampus impair acquisition and expression of trace-conditioned fear-potentiated startle in rats. *Behavioural Brain Research, 68*, 289–298.

Tse, D., Langston, R. F., Kakeyama, M., Bethus, I., Spooner, P. A., Wood, E. R., et al. (2007). Schemas and memory consolidation. *Science, 316*, 76–82.

Tulving, E. (1985). How many memory systems are there? *American Psychologist, 40*, 385–398.

van Kesteren, M. T., Rijpkema, M., Ruiter, D. J., & Fernandez, G. (2010). Retrieval of associative information congruent with prior knowledge is related to increased medial prefrontal activity and connectivity. *Journal of Neuroscience, 30*, 15888–15894.

Vetere, G., Restivo, L., Cole, C. J., Ross, P. J., Ammassari-Teule, M., Sheena, A., et al. (2011). Spine growth in the anterior cingulate cortex is necessary for the consolidation of contextual fear memory. *Proceedings of the National Academy of Sciences of the United States of America, 108*, 8456–8460.

Wang, S. H., Teixeira, C. M., Wheeler, A. L., & Frankland, P. W. (2009). The precision of remote context memories does not require the hippocampus. *Nature Neuroscience, 12*, 253–255.

Wiltgen, B. J., Sanders, M. J., Anagnostaras, S. G., Sage, J. R., & Fanselow, M. S. (2006). Context fear learning in the absence of the hippocampus. *Journal of Neuroscience, 26*, 5484–5491.

Wiltgen, B. J., & Silva, A. J. (2007). Memory for context becomes less specific with time. *Learning and Memory, 14*, 313–317.

Wiltgen, B. J., Wood, A. N., & Levy, B. (2011). The cellular mechanisms of memory are modified by experience. *Learning and Memory, 18*, 747–750.

Wiltgen, B. J., Zhou, M., Cai, Y., Balaji, J., Karlsson, M. G., Parivash, S. N., et al. (2010). The hippocampus plays a selective role in the retrieval of detailed contextual memories. *Current Biology, 20*, 1336–1344.

Winocur, G. (1990). Anterograde and retrograde amnesia in rats with dorsal hippocampal or dorsomedial thalamic lesions. *Behavioural Brain Research, 38*, 145–154.

Winocur, G. (1997). Hippocampal lesions alter conditioning to conditional and contextual stimuli. *Behavioural Brain Research, 88*, 219–229.

Winocur, G., Frankland, P. W., Sekeres, M., Fogel, S., & Moscovitch, M. (2009). Changes in context-specificity during memory reconsolidation: Selective effects of hippocampal lesions. *Learning and Memory, 16*, 722–729.

Winocur, G., & Gilbert, M. (1984). The hippocampus, context, and information processing. *Behavioral and Neural Biology, 40*, 27–43.

Winocur, G., McDonald, R. M., & Moscovitch, M. (2001). Anterograde and retrograde amnesia in rats with large hippocampal lesions. *Hippocampus, 11*, 18–26.

Winocur, G., & Moscovitch, M. (2011). Memory transformation and systems consolidation. *Journal of the International Neuropsycholical Society, 17*, 766–780.

Winocur, G., Moscovitch, M., & Bontempi, B. (2010). Memory formation and long-term retention in humans and animals: Convergence towards a transformation account of hippocampal–neocortical interactions. *Neuropsychologia, 48*, 2339–2356.

Winocur, G., Moscovitch, M., Caruana, D. A., & Binns, M. A. (2005). Retrograde amnesia in rats with lesions to the hippocampus on a test of spatial memory. *Neuropsychologia, 43*, 1580–1590.

Winocur, G., Moscovitch, M., Fogel, S., Rosenbaum, R. S., & Sekeres, M. (2005). Preserved spatial memory after hippocampal lesions: Effects of extensive experience in a complex environment. *Nature Neuroscience, 8*, 273–275.

Winocur, G., Moscovitch, M., Rosenbaum, R. S., & Sekeres, M. (2010). An investigation of the effects of hippocampal lesions in rats on pre- and postoperatively acquired spatial memory in a complex environment. *Hippocampus, 20*, 1350–1365.

Winocur, G., Moscovitch, M., & Sekeres, M. (2007). Memory consolidation or transformation: Context manipulation and hippocampal representations of memory. *Nature Neuroscience, 10*, 555–557.

Winocur, G., & Olds, J. (1978). Effects of context manipulation on memory and reversal-learning in rats with hippocampal-lesions. *Journal of Comparative and Physiological Psychology, 92*, 312–321.

Winocur, G., Rawlins, J. N., & Gray, J. A. (1987). The hippocampus and conditioning to contextual cues. *Behavioral Neuroscience, 101*(617–625), 742.

Winocur, G., Sekeres, M. J., Binns, M. A., & Moscovitch, M. (2013). Hippocampal lesions produce both nongraded and temporally graded retrograde amnesia in the same rat. *Hippocampus, 23*, 330–341.

Winocur, G., Wojtowicz, J. M., Sekeres, M., Snyder, J. S., & Wang, S. (2006). Inhibition of neurogenesis interferes with hippocampus-dependent memory function. *Hippocampus, 16*, 296–304.

Wojtowicz, J. M., Askew, M. L., & Winocur, G. (2008). The effects of running and of inhibiting adult neurogenesis on learning and memory in rats. *European Journal of Neuroscience, 27*, 1494–1502.

Young, S. L., Bohenek, D. L., & Fanselow, M. S. (1994). NMDA processes mediate anterograde amnesia of contextual fear conditioning induced by hippocampal damage: Immunization against amnesia by context preexposure. *Behavioral Neuroscience, 108*, 19–29.

Zelikowsky, M., Bissiere, S., & Fanselow, M. S. (2012). Contextual fear memories formed in the absence of the dorsal hippocampus decay across time. *Journal of Neuroscience, 32*, 3393–3397.

Zhang, W. N., Bast, T., & Feldon, J. (2001). The ventral hippocampus and fear conditioning in rats: Different anterograde amnesias of fear after infusion of N-methyl-D-aspartate or its noncompetitive antagonist MK-801 into the ventral hippocampus. *Behavioral Brain Research, 126*(1–2), 159–174.

Zola-Morgan, S., & Squire, L. R. (1985). Medial temporal lesions in monkeys impair memory on a variety of tasks sensitive to human amnesia. *Behavioral Neuroscience, 99*, 22–34.