Psychological Bulletin
2004, Vol. 130, No. 6, 843–857

0033-2909/04/$12.00 DOI: 10.1037/0033-2909.130.6.843

Consolidation of Long-Term Memory: Evidence and Alternatives

Martijn Meeter
Vrije Universiteit Amsterdam and University of Amsterdam

Jaap M. J. Murre
University of Amsterdam and University of Maastricht

Memory loss in retrograde amnesia has long been held to be larger for recent periods than for remote periods, a pattern usually referred to as the *Ribot gradient*. One explanation for this gradient is consolidation of long-term memories. Several computational models of such a process have shown how consolidation can explain characteristics of amnesia, but they have not elucidated how consolidation must be envisaged. Here findings are reviewed that shed light on how consolidation may be implemented in the brain. Moreover, consolidation is contrasted with alternative theories of the Ribot gradient. Consolidation theory, multiple trace theory, and semantization can all handle some findings well but not others. Conclusive evidence for or against consolidation thus remains to be found.

Consolidation, as a concept, has a century-old history (Lechner, Squire, & Byrne, 1999). It was originally proposed as an explanation for retroactive interference (Muller & Pilzecker, 1900). Although interference theory soon came to rely on other constructs (McGeoch, 1932), consolidation fanned out to explain a plethora of other phenomena. A search in PsycLIT in August 2003 focusing on consolidation and memory, for example, produced 1,167 hits, of which more than a quarter were from the period since 2000.

Consolidation is perhaps most often suggested as an explanation for the gradient in retrograde amnesia (Alvarez & Squire, 1994; McClelland, McNaughton, & O'Reilly, 1995; Murre, 1996). After damage to the hippocampal memory system, patients tend to lose more of their recent than of their remote memories (Kim & Fanselow, 1992; Kopelman, 1989; Squire, 1992). This pattern is referred to here as the Ribot gradient after Theodule Ribot, who first suggested that recent memories might be more vulnerable to brain damage than remote memories (Ribot, 1881). The Ribot gradient can be explained by assuming that memories are first dependent on a hippocampal memory system for their retrieval. Through consolidation, memories gradually become stored in the neocortex, making them independent of the hippocampal system (Squire & Alvarez, 1995; Squire, Cohen, & Nadel, 1984). If the hippocampal system is damaged, recent memories are lost, because they still depend on that system. Old memories have already been stored in the neocortex through consolidation and are thus spared.

Martijn Meeter, Department of Cognitive Psychology, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands, and Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands; Jaap M. J. Murre, Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands, and Department of Computer Science, University of Maastricht, Maastricht, the Netherlands.

This research was supported by a PIONIER grant from the Netherlands Society for Scientific Research to Jaap M. J. Murre.

Correspondence concerning this article should be addressed to Martijn Meeter, Department of Cognitive Psychology, Vrije Universiteit Amsterdam, Vd Boechorststraat 1, 1018 BT Amsterdam, the Netherlands. E-mail: m@meeter.nl

Although most consolidation theorists agree on the outlines of the process, many details remain vague. The precise time course of consolidation is unclear, and when it takes place and how it occurs remain speculative. Partly for this reason, but mainly as a result of a thorough and intelligent critique by Nadel, Moscovitch, and colleagues (Nadel & Moscovitch, 1997; Nadel, Samsonovitch, Ryan, & Moscovitch, 2000), consolidation theory has become controversial in the past few years. Here we review what is known about consolidation and the arguments that have been forwarded for its existence. In addition, we discuss two alternative explanations for the Ribot gradient and compare these explanations with consolidation theory.

What Is Long-Term Consolidation?

Long-term memory consolidation is not the only process for which the term is used. The different phenomena that have been labeled consolidation in the literature occur at widely varying time scales (Squire & Alvarez, 1995). Consolidation on the shortest time scales refers to a biochemical process of "fixing." It is invoked in the amnesia literature to explain the short, dense retrograde amnesia that often occurs after blunt head injury (Kapur, 1999; Lynch & Yarnell, 1973; Whitty & Zangwill, 1977). This immediate preonset amnesia (or "pre-ictal amnesia"; Kapur, 1999) can be dissociated from the diffuse or patchier retrograde amnesia that can also result from trauma and that may extend over much longer periods of time (Kapur, 1999; Williams & Zangwill, 1952). The most likely explanation for immediate preonset amnesia involves a short-term fixing mechanism that operates in the minute range, with which the concussion interferes (McGaugh, 2000).

On a somewhat longer time scale, there is evidence for a process of reorganization that takes several hours and is sometimes referred to as consolidation. Karni and Sagi (1993) found that after people learn a visual skill, their performance improves substantially after a delay of 8 hr or more. They referred to the process underlying this improvement as consolidation. Similar processes, on a scale of hours and also referred to as consolidation, seem to occur in motor learning (Shadmehr & Holcomb, 1997). In the animal literature (e.g., Tiunova, Anokhin, & Rose, 1998), the term

may refer to a process of biochemical reorganization in the synapse that occurs in the hours following learning and with which inhibitors of protein synthesis may interfere. Such a phase can last a few hours; memory for place avoidance can, for example, be blocked by infusions of the hippocampus with protein synthesis blockers for up to 6 hr after learning (Muller Igaz, Vianna, Medina, & Izquierdo, 2002). This process of protein synthesis has been termed *cellular consolidation* (Dudai & Morris, 2000).

Cellular consolidation or processes operating at even shorter time scales are not the consolidation that is invoked to explain the Ribot gradient. Because these gradients stretch over months and years, underlying memory consolidation must also take months or years (see Figure 1). This hypothetical process transforms a memory from being dependent on the hippocampus to being independent of that structure (Marr, 1971; Squire, 1992; Squire et al., 1984). Although it is tempting to speak of a transfer of memories from one store to another, this is not what most theorists have in mind when they think of consolidation, and it would also not be in agreement with the facts (e.g., Izquierdo et al., 1997). Memories are usually envisaged as stored in the neocortex, but at first "bound" together by the hippocampus. Consolidation, then, is the strengthening of connections within the neocortex to the extent that these connections suffice for retrieval (Milner, 1989; Paller, 1997; Squire & Alvarez, 1995; Teyler & DiScenna, 1986; Wittenberg & Tsien, 2002), as can be seen in Figure 2. This is also how extant models of memory consolidation have implemented the process (Alvarez & Squire, 1994; McClelland et al., 1995; Meeter, 2003; Meeter & Murre, 2004, in press; Murre, 1996).

Consolidation in Connectionist Models

The three models that have simulated corticohippocampal interactions (Alvarez & Squire, 1994; McClelland et al., 1995; Murre, 1996) shed some light on these processes, even though they do not elucidate the details of the mechanisms underlying consolidation. The basic assumption they share is that there is a fast-learning hippocampal memory system, and a neocortical memory system in which representations are gradually built up during consolidation. This is implemented as a process of rehearsal, in which stored patterns are strengthened or repaired by rehearsing with patterns themselves (McClelland et al., 1995; Robins, 1995), or as "pseudorehearsal," in which patterns are generated from the network by means of random cues (Alvarez & Squire, 1994; Meeter & Murre, in press; Murre, 1996; Robins, 1996). These patterns are then interleaved with new patterns to protect, repair, or strengthen old ones. In TraceLink, for example (Meeter & Murre, 2004, in press; Murre, 1996), the neocortical memory system is a large layer in which only weak connections are laid between nodes belonging to one pattern. Consolidation is simulated by allowing the model, from an initial random state, to relax into an attractor (i.e., retrieving an existing memory) and then updating the weights with a Hebbian learning rule. Eventually, the connections between neocortical nodes built up during consolidation allow the patterns to be retrieved without the support of the hippocampal system.

Consolidation is thus modeled as the strengthening of connections within a neocortical pattern that is retrieved through the hippocampal system. This implies that there must be consolidation phases in which the hippocampal system reinstates patterns in neocortical memory areas. Furthermore, such a consolidation phase may lead to higher retrievability of the pattern, because consolidation in the TraceLink model is equivalent to additional learning. Experimental techniques should thus be able to detect small effects of improved performance on memory tasks after consolidation (this would not have to be the case if consolidation were a pure reorganization process).

A more detailed analysis of the models leads to other constraints. For example, consolidation is sensitive to "runaway consolidation," a vicious circle in which one pattern becomes stronger through consolidation, becomes more likely to be consolidated in

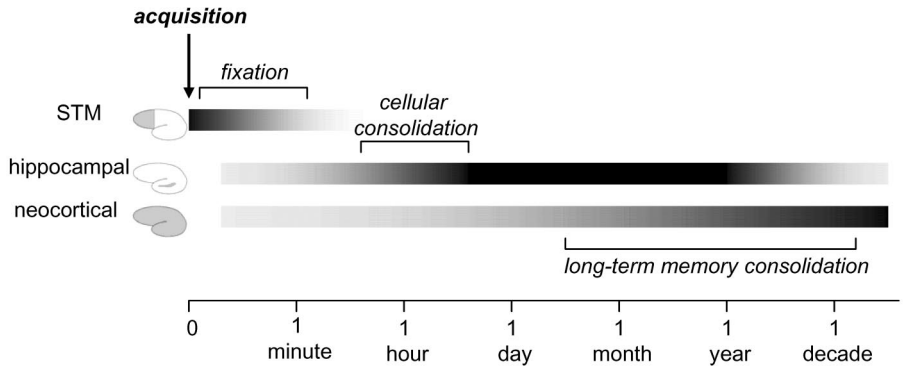

Figure 1. Life cycle of a human memory acquired at time = 0 on a pseudologarithmic scale. Darkness of tone indicates involvement of a memory system in retrieval. Memories are first held in short-term memory/working memory (STM), which is generally thought to rely on a network centered on the frontal lobes. If the memory has to be retrieved at this stage, this will be done through STM. Within minutes, memories are stored in long-term memory (hippocampus and neocortex) through a process of fixing. In subsequent hours, a process of cellular consolidation stabilizes the memory. Long-term memory consolidation is thought to start thereafter, and it involves a strengthening of the memory in the neocortex. Accompanying this is a weakening of memories in the hippocampus. Whereas retrieval will involve both the hippocampus and the neocortex in the intermediate term (days to years), it may come to depend solely on the neocortex after consolidation.

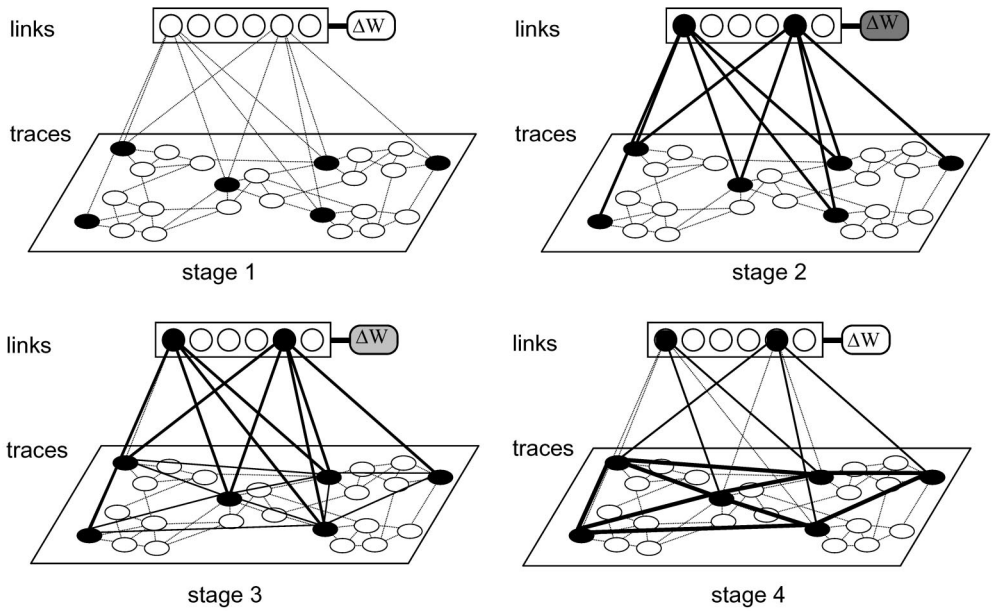

Figure 2. View of how consolidation contributes to memory, as incorporated in the TraceLink model (Meeter & Murre, in press; Murre, 1996). TraceLink consists of three systems: neocortical memory repository (trace system), a temporary medial–temporal lobe memory store (link system), and a system regulating the link system's plasticity (modulatory system, indicated by ΔW for its control of learning rates). The normal formation of episodic memories is, for expository purposes, subdivided into four stages. Stage 1: A new memory representation activates a number of trace elements (shown as solid circles), symbolizing an episodic memory widely dispersed over the neocortex. Stage 2: Several link elements are activated by the trace representation. Also, the modulatory system has been activated, strengthening plasticity in the link system. Relevant trace–link connections are therefore quickly strengthened (shown as thicker connections). Stage 3: Weak trace–trace connections are developing through consolidation. The modulatory system is now not activated. Stage 4: Strong trace–trace connections have been formed, which can now sustain memory retrieval. Trace–link connections have decayed.

the next trial, and ends up monopolizing all consolidation resources while crowding out other memories (Meeter, 2003). In the models, runaway consolidation is avoided through the dominance of the hippocampal system, helping to reactivate patterns in the neocortex that have not yet benefited from consolidation (Alvarez & Squire, 1994; McClelland et al., 1995; Meeter & Murre, in press; Murre, 1996). If, during the reactivation, learning occurs within the hippocampal system, runaway consolidation immediately rears its head, in that now consolidated memories become stronger in both the hippocampus and the neocortex (Meeter & Murre, in press). Consolidation should therefore take place during a period in which the hippocampus is not very plastic.

Time Course of Consolidation

In simulations of consolidation, such as those with TraceLink, the time scale on which consolidation processes take place is not made explicit. In a sense, it remains a free parameter of the models. This has been a point of criticism of consolidation theory (Nadel & Moscovitch, 1997); in no way does consolidation offer any constraints on how long the process might require. As discussed later, alternative theories do not offer constraints on the time scale either. Unfortunately, the only hint about the time course of the consolidation process is the length of the Ribot gradient. Because that length can vary from days or weeks in rats (Izquierdo et al., 1997; Kim & Fanselow, 1992; Winocur, McDonald, & Moscovitch, 2001) to months in monkeys (Zola-Morgan & Squire, 1990) and years or decades in humans, consolidation may proceed faster in some species than in others (see McClelland et al., 1995, for estimates of speed of consolidation derived from model fitting). However, even within species the length of the Ribot curve can vary considerably (Murray & Bussey, 2001). In humans, for example, the length of the Ribot gradient can vary from a few years (Levin et al., 1985) to decades (Albert, Butters, & Levin, 1979; Mayes, Daum, Markowitch, & Sauter, 1997). Larger hippocampal system lesions may result in longer Ribot gradients (Nadel & Moscovitch, 1997), and length probably varies with age of the patient, type of lesion, type of material, and other variables. Empirical Ribot curves are mostly very noisy, and the length of the Ribot gradient is usually only eyeballed. Fitting of curves with a theoretically motivated mathematical model might improve clarity and, through the fitted parameters, finally provide more systematic estimates of the time course of consolidation and what it depends on.

Nadel and Moscovitch (1997) attacked not only the variety of durations of retrograde amnesia but also the length that they can have. Ribot curves can span well over 25 years (Albert et al., 1979;

Beatty, Salmon, Butters, Heindel, & Granholm, 1988; Squire, Haist, & Shimamura, 1989). A consolidation process lasting 25 years would, according to Nadel and Moscovitch (1997), stretch credulity, because for most of history humans did not live much longer than that. A transfer process lasting two thirds of a lifetime would not serve any purpose; for example, the idea that the hippocampus has limited capacity would lose its force as a ground for consolidation if, in fact, memories from a large part of our lives were stored in it. In the models of consolidation, most memory consolidation occurs in the first period after acquisition, but the models indeed seem to consolidate memories for as long as the simulation lasts (McClelland et al., 1995; Meeter & Murre, in press). This suggests that although consolidation might not be as intense after a decade as immediately after learning, if it is to explain the Ribot gradient in the way exemplified by the models, it must be a process lasting many years in humans.

Conscious and Unconscious Processes in Consolidation

As discussed earlier, consolidation has been implemented as the gradual strengthening, within the neocortex, of patterns retrieved with help of the hippocampus. This does not pin down how this occurs in the brain. It might be that it happens only with conscious rehearsal. Indeed, rehearsing a memory generally strengthens it, and retrieval also has a biochemical impact in the brain (Debiec, LeDoux, & Nader, 2002). However, if the external world provides all cues for rehearsal, it would be difficult to explain Ribot gradients in animals for tasks performed away from the home cage, such as the Morris water maze (Murray & Bussey, 2001; Nadel & Moscovitch, 1997; Squire, 1992). Because explicit rehearsal occurs either in response to cues from the environment or through reminiscence, we would thus be forced to grant conscious reminiscence to experimental animals such as rats and mice.

Another mechanism by which consolidation might operate is subconscious activation of memories (Murre, 1997). One could postulate that when a memory is retrieved, related memories become temporarily activated. Although they stay below the threshold of consciousness, this activation might lead to a strengthening of the cortical base of these related memories through processes that may also underlie semantic priming (i.e., the facilitation of one word through previous presentation of an associate, e.g., faster recognition of the word *dog* if the word *cat* has been presented previously). In this way, memories that are not rehearsed might be consolidated through rehearsal of associated memories. However, it is unclear whether semantic priming has effects that last longer than a few seconds (Zeelenberg & Pecher, 2002).

The most frequently proposed method of consolidation is rehearsal during sleep (Marr, 1971; McClelland et al., 1995; Robins & McCallum, 1999; Squire & Alvarez, 1995). The idea of consolidation during sleep has a long history, and a large body of circumstantial evidence has been amassed. For example, changes in sleep patterns have been noted after strong learning experiences. In one study, increases in REM sleep intensity were observed among students after a period of examinations (Smith & Lapp, 1991). Similarly, when animals are required to learn new tasks or are exposed to an enriched environment, they tend to spend more time in REM sleep (Hennevin, Hars, Maho, & Bloch, 1995). Subsequent sleep also is characterized by larger than usual biochemical activity connected to plasticity (Smith, 1996).

Psychological experiments have shown improvements in declarative memory after sleep (Ekstrand, 1967; Jenkins & Dallenbach, 1924; Van Ormer, 1932). Some studies have found slow-wave sleep to be helpful for declarative memory (Fowler, Sullivan, & Ekstrand, 1973; Philal & Born, 1997), whereas others have found the effects to depend more on REM sleep (Smith, 1996). Striking improvements after sleep have been noted in simple skills (Stickgold, James, & Hobson, 2000). Critics have questioned whether REM sleep has a role in memory, however (Blagrove, 1991; Siegel, 2001; Vertes & Eastman, 2000): Total elimination of REM sleep, as produced by a widely used class of antidepressants—monoamine oxidase inhibitors—does not notably affect memory function in humans (Siegel, 2001). Other researchers have suggested that this may be true only in the case of declarative memory and that REM sleep is important for procedural learning (Stickgold, Hobson, Fosse, & Fosse, 2001).

Slow-wave sleep is perhaps the most viable candidate for the phase in which consolidation of declarative memory occurs. Synaptic transmission in the hippocampus tends to be more efficient during slow-wave sleep (Squire & Alvarez, 1995), while at the same time plasticity is reduced in the hippocampus (Hasselmo, 1999; Jones Leonard, McNaughton, & Barnes, 1987). As already discussed, this is what models of consolidation would require for the proposed consolidation process to occur during sleep. Moreover, several studies have shown that hippocampal neurons active during daytime tasks are reactivated in slow-wave sleep (Nadasdy, Hirase, Czurko, Csicsvari, & Buzsaki, 1999; Pavlides & Winson, 1989; Skaggs & McNaughton, 1996; Sutherland & McNaughton, 2000; Wilson & McNaughton, 1994). Wilson and McNaughton (1994), for example, monitored hippocampal cell activity in rats with multielectrode recordings. They showed that cells that had been active concurrently during a period of spatial exploration tended to become active in a correlated fashion again during a subsequent episode of deep sleep. Memories thus seem to be reactivated during sleep. Such "replay" activity has also been found in REM sleep (Louie & Wilson, 2001; Poe, Nitz, McNaughton, & Barnes, 2000) and even in quiet waking (provided that ripple activity is seen in the hippocampus; Kudrimonti, Barnes, & McNaughton, 1999).

An indication that these hippocampal reactivations drive the neocortex during slow-wave sleep has also been found. Qin, McNaughton, Skaggs, and Barnes (1997) recorded hippocampal and neocortical cell activity with the same multielectrode devices used by Wilson and McNaughton (1994). Analyzing correlations between cell firing, the authors showed slow-wave sleep replay of daytime activities not only in the hippocampus but also in the parietal lobe of the neocortex. Moreover, hippocampal and neocortical cells that had been active together during waking were also active together during sleep (Qin et al., 1997). The temporal order in which such cell pairs fired was not preserved, unlike that between cell pairs within the hippocampus or within the neocortex. In line with consolidation theory, the authors explained this by noting that during waking the neocortex may drive the hippocampus, whereas during sleep this situation may be reversed.

There is also evidence for cortical reorganization in sleep. In young cats, investigators covered one eye for 6 hr and observed how visual cortex neurons responsive to this eye became responsive to the other eye. The amount of change in firing properties in the neurons was correlated with the amount of slow-wave sleep

that the kittens received (Frank, Issa, & Stryker, 2001). Although there is no indication that the hippocampus played a role in this reorganization, the results show that changes in neocortical representations may take place during sleep.

All conditions on consolidation set by current models such as TraceLink thus seem to be fulfilled during slow-wave sleep. There is evidence that during slow-wave sleep traces of recent experiences are reactivated spontaneously in the hippocampus, that hippocampal and neocortical memories are reactivated together, that hippocampal plasticity is low, that neocortical representations can be reorganized, and that memory may improve. Nevertheless, it is not yet beyond doubt that the reactivations seen in slow-wave sleep constitute consolidation processes (Sutherland & McNaughton, 2000). No learning has, for example, been shown to take place during these reactivations. Moreover, reactivation has, until now, been studied only in sleep episodes immediately following the behavior that forms the criterion. In other words, findings do not address whether consolidation lasts longer than a single day, which would be expected from the length of the Ribot gradient even in rodents (Squire, 1992). In summary, the contribution of conscious, subconscious, and sleep-induced processes of rehearsal to consolidation is still an open question, though one with promising leads.

Evidence

In spite of its somewhat speculative status, the hypothesis that memories are consolidated in the neocortex attracts a large and continuing following. Its main attraction is the explanation it offers for the Ribot gradient and other findings from neuropsychology. This explanation is not very parsimonious, as a new process is assumed to explain a single data pattern. In the past decade, however, support from other sources than neuropsychology has started to accumulate. We first discuss imaging studies and neurobiological findings that support consolidation theory and then review the neuropsychological evidence.

Evidence From Functional Imaging

If the hippocampal memory system plays a time-limited role in memory, a central tenet of consolidation theory, then retrieval of recent and remote memories should differentially tax the hippocampus. This logic has led to at least six functional imaging studies, five of which involved human participants and one of which involved experimental animals.

Of the studies with humans, two yielded data consistent with consolidation theory, and two did not. The latter two studies compared brain activity during retrieval of recent memories with that during retrieval of remote autobiographical memories using functional magnetic resonance imaging (fMRI). Both studies showed that hippocampal activation during retrieval was unaffected by age of the memory (Maguire, Henson, Mummery, & Frith, 2001; Ryan et al., 2001), and one produced the same result for questions about the news (Maguire et al., 2001). A third study also compared memory for recent and remote public knowledge with fMRI but did reveal evidence for a time-limited role of the hippocampus (Haist, Bowden Gore, & Mao, 2001). In this study, people were shown faces of people of recent fame (i.e., who were famous in the 1980s and 1990s) and faces of people who had been famous in earlier decades (1940s to 1970s). There was a small increase in right hippocampal complex activity with recent famous faces relative to the remote famous faces. The fourth study, also using fMRI, investigated retrieval of memories for topographic locations (Niki & Luo, 2002). Places visited in the past 1.5 years were compared with places visited at least 7 years in the past. Recall of the more recent visits was associated with larger medial–temporal lobe activation relative to the more remote visits, "peaking in the left parahippocampal gyrus" (Niki & Lou, 2002, p. 501). The fifth study, the only one to use positron emission tomography, failed to reveal differential hippocampal activation in any retrieval condition and therefore is not informative as to whether the hippocampus is more involved in recent or remote memory retrieval (Conway et al., 1999).

All of the studies discussed involved drawbacks that make conclusions difficult. For example, memories used in the study were often elicited from the participants in a session a few weeks (Maguire et al., 2001), days (Niki & Luo, 2002), or hours (Ryan et al., 2001) before the scanning, which means that recall from this session may have played a role, mitigating any age effect. Moreover, activation of the hippocampus during retrieval of remote memories may partly reflect learning about the retrieved remote memories (Niki & Luo, 2002; Ryan et al., 2001), and the task used by Maguire et al. (2001) may have been too undemanding (Niki & Luo, 2002).

Also, for other reasons it is not clear what to make of the inconsistent results. Effects were small in the studies that did find them, and a null finding can always be a matter of lack of power (indeed, with the public events questions used by Maguire et al., 2001, a small trend toward greater activation of the hippocampus with recent memories was apparent). Moreover, there were many task differences that may explain the differences in results (e.g., it is striking that the studies finding differential hippocampal activation used visual stimuli and descriptions of places, whereas the other two relied on verbal questions).

There is also a conceptual problem with the studies. The logic of the experiments assumes that if the hippocampus is *active* during the retrieval of remote memories, it must *underlie* that retrieval. However, the hippocampus is also massively active during simple classical eyeblink conditioning (e.g., Berger & Thompson, 1978), although the eyeblink conditioned response is actually acquired faster after hippocampal lesions (Schmaltz & Theios, 1972). Thus, hippocampal activity during retrieval of remote memories might, as in the case of classical conditioning, reflect processing that is essentially superfluous in terms of performance. A finding of similar hippocampal activity in the retrieval of remote and recent memories is therefore not a falsification of consolidation theory. A finding of more activity in the retrieval of recent than of remote memories is informative, because it is consistent with consolidation theory and not a trivial result.

Perhaps the strongest study showing such a pattern was the sixth, involving animals (Bontempi, Laurent-Demir, Destrade, & Jaffard, 1999). Mice were trained on a radial arm maze discrimination problem, with a recall test occurring either 5 or 25 days after most recent training. Brain activity was measured after recall by means of a radioactive tracer. After the short interval, hippocampal activity was predominant, whereas after the long interval, no hippocampal activity was found (as compared with quiet controls). Instead, the temporal frontal and anterior cingulate neocortex were activated. These results are in line with what would be expected

from consolidation theory. Ryan et al. (2001) offered as an alternative explanation for the results that retention interval was confounded with performance, and worse performance for the remote memories may thus have caused the lower hippocampal activation. However, this explanation ignores the recruitment of neocortical areas in recall after the long interval, along with the fact that performance was strongly correlated (.69, $p < .05$) with hippocampal activation after the short interval but not at all after the long interval (instead, it correlated with frontal cortex and nucleus accumbens activation). At the least, the results thus support that there is a switch from hippocampus-based retrieval to cortex-based retrieval.

Evidence From Neurobiology

A temporary role of the hippocampus in memory, as indicated by the Ribot gradient and the Bontempi et al. (1999) findings, has also gained support from several neuropharmacological studies. In one such study, rats were trained to locate a hidden platform in a water maze (Atlantis platform) and then tested 16 days later (Riedel et al., 1999). Hippocampal activation was blocked after training with an AMPA receptor antagonist (LY326325). This was done either in the first 7 days after training or from the fifth to the seventh day after training. At test, 16 days after acquisition, control rats spent a significant amount of time swimming in the quadrant in which the platform had been located (but from which it was removed for the test). Rats whose hippocampal activity was blocked, however, swam at random independent of when the AMPA antagonist was administered. This was not due to residual effects of LY326325, in that the animals readily learned, on the same day as the test, the location of a platform in a new water maze. Consolidation theory can explain these findings by assuming that the temporary deactivation of the hippocampus blocked memory consolidation, leading to a loss of task-relevant memories.

In another study, rats were trained in a step-down inhibitory avoidance task (Izquierdo et al., 1997). The animals were tested after a retention interval of 1 day, 30 days, or 60 days. Before the test, an AMPA receptor blocker (CNQX) was injected in one of three regions: the hippocampus and amygdala, the entorhinal cortex, or the parietal lobe of the neocortex. When a 1-day interval was used, injections of CNQX in any of the three regions could block performance. After 30 days, only injections in the entorhinal and parietal cortices affected performance; the hippocampus and amygdala had ceased to be of critical value. After a retention interval of 60 days, only injections in the parietal cortex still had an effect on performance. These data seem in line with consolidation theory, in that memories are stored at acquisition in the neocortex (here the parietal cortex) and the hippocampal system. Directly after learning, the hippocampal system representation is needed for retrieval, but 2 months after learning the representation in the neocortex can sustain retrieval on its own.

Other evidence comes from a study (Frankland, O'Brien, Ohno, Kirkwood, & Silva, 2001) in which wild-type mice were compared with mice that had a mutation resulting in severely impaired long-term potentiation (LTP) in the neocortex (hippocampal LTP remained intact). The mice with impaired neocortical LTP were able to acquire new memories to the same degree as wild-type mice, as assessed by several tasks, but forgot them at a much higher speed than the normal mice. Consolidation theory can explain these data as follows: Although memories can be acquired via the hippocampus, they are forgotten more rapidly because of inadequate consolidation in the neocortex.

The three studies just described all seem to deliver strong support for consolidation theory. In the case of two of these studies, however, alternative explanations are possible. In the Riedel et al. (1999) study, 5 days of deactivation may have led to the loss of all memories from the hippocampus, independent of age and independent of consolidation. In the Frankland et al. (2001) study, it may have been that both the hippocampus and the neocortex store memories in a way sufficient for retrieval in wild-type mice. If hippocampal memories are forgotten relatively swiftly (an assumption of consolidation theory), then animals relying on only the hippocampus would show faster forgetting than animals relying on both the hippocampus and neocortex. In other words, the Frankland et al. study does not allow us to decide between a consolidation account (from hippocampus-based to cortex-based retrieval) and a dual storage account (both hippocampus and cortex). For the Izquierdo et al. (1997) study, that second account is not possible, however, because it does not explain why at shorter intervals a lesion of the hippocampus or entorhinal cortex disrupts performance. Of the mentioned studies, this one thus offers the strongest support for consolidation theory.

One other pertinent study is at best only consistent with consolidation. In a design similar to that of Riedel et al. (1999), Shimizu, Tang, Rampon, and Tsien (2000) trained mice on a Morris water maze and then blocked *N*-methyl-D-aspartate (NMDA) receptors in field CA1 of the hippocampus in the first 4 days after training. This led to a small loss in performance 12 days later. Performance was not affected by NMDA blockers delivered in the 3 days before the test, starting 12 days after training. Shimizu et al. (2000) viewed their data as evidence for consolidation occurring within the hippocampus, instead of between the hippocampus and the neocortex. Consolidation theory as it has been modeled is not consistent with plasticity in the hippocampus during consolidation, which suggests that the findings are at odds with consolidation theory. However, NMDA receptors play an important role not only in plasticity but also in transmission of signals (Phillips & Silverstein, 2003). It is thus possible that the results of Shimizu et al. (2000) do not reflect the effects of blocking plasticity, but of hindering transmission in the hippocampus during memory consolidation. This would make the results consistent with consolidation theory.

Evidence From Neuropsychology

The strongest argument for long-term memory consolidation remains the existence of the Ribot gradient. Although other explanations are possible, the consolidation hypothesis provides a simple and compelling reason for the gradient. Skeptics of consolidation have, for that reason, often been skeptical of the gradient as well. Nadel and Moscovitch (1997), for example, claimed that ungraded memory loss is just as frequent as graded memory loss, and they listed a number of studies in which patients with damage limited to the hippocampal region exhibited either flat retrograde amnesia or amnesia with a very shallow gradient. In one recent study, a patient with lesions restricted to the hippocampus showed a flat loss of memories in episodic retrieval tests, although a gradient was evident in personal semantic memory (Cipolotti et al.,

2001). Such findings are problematic for consolidation theory and can be explained only with an ad hoc assumption of undetected neocortical malfunctioning (Squire & Alvarez, 1995), inadequate sampling of memories, or a psychogenic component of the amnesia (in that psychogenic retrograde amnesia tends to be extensive and ungraded; Kopelman, 1994).

Nevertheless, the gradient has been found many times in both human and animal studies (Anagnostaras, Gale, & Fanselow, 2001; Brown, 2002; Kim & Fanselow, 1992; Kopelman, 1989; Rempel-Clower, Zola, Squire, & Amaral, 1996; Squire, 1992), and Nadel and Moscovitch (1997) also seemed of the opinion that these studies warrant an explanation. Moreover, other characteristics of amnesia are easily explained by consolidation theory. Examples are the intactness of many forms of implicit memory in amnesia, the shrinking of transient retrograde amnesia, and the high but not perfect correlation between anterograde and retrograde amnesia[1] (Meeter & Murre, in press).

Patterns in the episodic memory of semantic dementia patients are also easy to understand in the light of consolidation theory (Graham, 1999; Meeter & Murre, 2004; Murre, Graham, & Hodges, 2001). Patients with semantic dementia show atrophy of the temporal neocortex, with, according to initial reports, a sparing of the hippocampus. Remote memory in semantic dementia assumes an "inverse gradient": a loss of distant memories with relative preservation of more recently experienced memories (Graham, Becker, & Hodges, 1997; Snowden, Griffiths, & Neary, 1996). This characteristic of semantic dementia was predicted by Murre (1996) from consolidation theory. It can be understood as the result of a damaged neocortical store of remote memories, with an intact hippocampal store of recent memories. The relative intactness of episodic learning in semantic dementia also follows naturally from this view.

In different ways, data from human retrograde amnesia and semantic dementia and data from retrograde amnesia in experimental animals are open to methodological critique. If gradients in retrograde amnesia and semantic dementia are the result of a methodological caveat, then the ground for supposing a consolidation mechanism would fall away.

Neuropsychological data are often noisy as a result of small sample sizes and considerable interpatient heterogeneity. Many neuropsychological tests are also complex, tasking many skills at once. Studies of retrograde amnesia are no exception. A thorough test of consolidation theory is possible only among patients whose lesions are, to a large extent, limited to the hippocampal complex. Patients with such lesions among whom retrograde amnesia has been assessed can be counted on perhaps three hands, and it is never the case that the rest of the brain is normal (Nadel & Moscovitch, 1997; Reed & Squire, 1998; Rempel-Clower et al., 1996).

Moreover, construction of tests of retrograde amnesia is fraught with difficulties. Tests for retrograde amnesia come in many formats, but for the analysis of gradients one characteristic is most important: the variable on which items from different periods in the test are equated. This variable can be either acquisition strength or retrieval probability. In both cases "item difficulty" is equalized, but at different points in time: either at acquisition or at recall. If test items are equated in regard to mean acquisition strength, memories are chosen in such a way that it is a priori plausible they were learned with the same strength. Examples are a test in which questions were asked about television series that had run just one season (Squire & Slater, 1975) and a test in which questions about news events were formulated according to a tight script from newspaper headings (Leplow et al., 1997). In such cases, interpretation of gradients is relatively straightforward. Test items can also be equated on retrieval probability, by verifying that a norm population has an equal score on all periods in the test (if assessment of a Ribot gradient is an important goal, a slight forgetting gradient is also acceptable). In this case, however, items from different time periods must differ. Items from remote periods have survived a long retention interval. When they nevertheless have a retrieval probability equal to that of items from more recent periods, these remote items must have had a higher acquisition strength than recent items. This difference may be simply quantitative, but it may also be qualitative. Remote items might, for example, be more "semantic" and recent items more "episodic" (definitions of these terms are provided later). Such differences may then explain why the remote items in the test are less affected by retrograde amnesia than the recent items (Cermak, 1984).

In fact, all studies that we are aware of with patients whose lesions were putatively limited to the hippocampus involved tests of the second kind, in which items were equated on retrieval probability. There is thus a possibility that this feature of retrograde amnesia tests explains the Ribot curve. However, if some qualitative difference makes recent items more difficult than remote items, it becomes very puzzling why there are systematic differences in gradients between different patient groups. Patients with Korsakoff's disease generally show steeper gradients than patients with Alzheimer's disease (Kopelman, 1989), both Parkinson's disease and Huntington's disease tend to show flat gradients in retrograde amnesia (Albert, Butters, & Brandt, 1981; Beatty et al., 1988; Leplow et al., 1997), and patients with semantic dementia show a reverse gradient (Graham & Hodges, 1997; Hodges & Graham, 1998; Snowden et al., 1996). Such differences are puzzling if, for methodological reasons, one should expect a Ribot gradient in all patients with remote memory impairment.

With regard to semantic dementia, some discussion has ensued as to whether it genuinely offers support for consolidation theory or not (Graham, Patterson, Pratt, & Hodges, 1999; Moscovitch & Nadel, 1999). Moscovitch and Nadel (1999) have claimed that it does not; in their view, remote memories are not affected any more

[1] Consolidation theory predicts a correlation between impaired learning (anterograde amnesia) and loss of recent memories (graded retrograde amnesia), in that both depend on the intactness of the hippocampal memory system. Empirically, the correlation tends to fall between .3 and .6 in groups of patients with degenerative diseases or with mixed etiology (Kopelman, 1989; Mayes et al., 1997; Schmidtke & Vollmer, 1997; Squire et al., 1989). From the data reported by Russel and Nathan (1946), gamma correlations of .77 and .68 can be computed for patients with concussions. In all of these cases, lesion heterogeneity may lower the correlation relative to its predicted value (e.g., the TraceLink model of consolidation explains disproportionate anterograde amnesia as arising out of basal forebrain damage; Meeter & Murre, in press). Series of patients with damage limited to the hippocampus are too small to allow meaningful correlational analyses. However, when one orders the 8 patients reported by Squire and colleagues according to extent of retrograde amnesia, this ordering corresponds perfectly with that of both the extent of anterograde amnesia and the size of the lesion (Reed & Squire, 1998; Rempel-Clower et al., 1996).

than recent memories in semantic dementia. Gradients reported in the literature, with test performance being lower for remote periods than for recent periods, could result from a greater difficulty of old versus new test items. These differences are, they claim, masked in the performance of normal controls by ceiling effects (Nadel et al., 2000).

Although not on all tests of remote memory, controls perform close to ceiling (e.g., incident items of the Autobiographical Memory Interview in Graham & Hodges, 1997), two other developments have seriously undermined the consolidation story of semantic dementia. First, careful volumetric analysis has undermined the view that the hippocampi are spared in semantic dementia; in fact, hippocampal damage may be as extensive as in Alzheimer's disease (Galton et al., 2001). Second, it has become clear that episodic learning is not normal in patients with semantic dementia, but extraordinarily sensory in nature. Although patients can recognize pictures of objects shown earlier nearly as well as normal controls can, their performance drops to a level close to that of patients with Alzheimer's disease when the perspective on the pictures is changed (Graham, Simons, Pratt, Patterson, & Hodges, 2000): The visual match seems essential in their recognition performance. In a similar vein, Nadel et al. (2000) have claimed that typical tests overestimate retrograde amnesia in semantic dementia because of a reliance on verbal cuing to the detriment of visual cuing of memories. They supported this claim with observations from a patient with semantic dementia who, with the help of visual cues, could be made to remember his wartime memories of more than half a century earlier (Nadel et al., 2000; see also Moss, Kopelman, Cappelletti, de Mornay Davies, & Jaldow, 2003; Westmacott, Leach, Freedman, & Moscovitch, 2001). Whether or not the reverse gradient is a real pattern would thus seem to depend on whether it can also be found with visual cues. Such research has yet to take place on a large scale.

With regard to studies with experimental animals, the situation is clearer. Animal studies do not suffer from a number of the drawbacks of the human studies; experimenters have full control over lesion size and can precisely control how long before surgery they train animals on a task. Nevertheless, it is only in the past 20 years that animal work has started to weigh in on the retrograde amnesia discussion. Of approximately 15 pertinent studies performed during that period, a clear majority have revealed Ribot gradients (Murray & Bussey, 2001; Nadel & Bohbot, 2001; Squire, Clark, & Knowlton, 2001). Some have not, and it is not yet clear what explains these conflicting results. Murray and Bussey (2001) listed a number of factors that may play a role, such as the use of within-subject versus between-subjects designs (with the former yielding more Ribot gradients but being more open to alternative explanations) and type of lesion (with more limited lesions favoring a Ribot gradient). However, studies involving between-subjects designs and complete lesions of the hippocampus have also demonstrated Ribot gradients (Clark, Broadbent, Zola, & Squire, 2002; Winocur et al., 2001).

In summary, remote memory gradients in semantic dementia will need more research for firm conclusions. In human and animal studies of retrograde amnesia, however, the onus seems to be squarely on those who want to disqualify the Ribot gradient, although methodological confounds cannot be wholly excluded.

Empirical Challenges to the Ribot Gradient

Two recent findings have muddied the water, however, in both the human and animal retrograde amnesia literatures. On the human side, a study appeared of three patients who had grown up with extensive hippocampal damage incurred during childhood (Vargha-Khadem et al., 1997). Although all three had quite strong amnesia, as assessed by standard episodic memory tests, they had done reasonably well in normal schools and had gained a substantial basis of general knowledge. These findings have led some to suggest that there are two ways of acquiring general knowledge: rapid, hippocampus-dependent learning and slow, neocortical learning (Holdstock, Mayes, Isaac, Gong, & Roberts, 2002). This is not inconsistent with consolidation theory, as consolidation theorists have already assumed slow, implicit learning in the neocortex (Meeter & Murre, in press). Others have argued against two ways of learning, suggesting that residual episodic memory is in all three cases enough to explain acquired knowledge (Squire & Zola, 1998). Whether or not this is the case, the patients described by Vargha-Khadem et al. (1997) do not seem to present a serious challenge to consolidation theory.

In the animal literature, the reemergence of "reconsolidation" has complicated the picture. Electroshocks to the brain have a greater effect on recent memories than on remote ones, producing graded amnesia after electroconvulsive therapy (Squire, Slater, & Chace, 1975). It has long been known that older memories, normally immune to electroshocks, can become vulnerable again when they are retrieved just before the shocks (Misanin, Miller, & Lewis, 1968). Somehow, reactivation makes a memory susceptible to amnesic treatments; it has to be "reconsolidated" to reenter in an invulnerable state.

The destabilizing effect of retrieval has been tied to the amygdala (Nader, Schafe, & LeDoux, 2000) and, recently, to the hippocampus. Debiec et al. (2002) elicited contextual fear in rats by administering shocks in a distinct context. The test occurred 4 days later. On the day before the test, some rats were exposed to the context as a reminder and subsequently infused with the protein synthesis blocker. This produced a large drop in contextual fear; without a reminder, the protein synthesis blocker had no effect on performance. The reminder thus brought the fear memory into a vulnerable state in which protein synthesis was necessary to maintain the memory. Protein synthesis was necessary in the hippocampus, even after a 45-day interval that normally makes contextual fear memories independent of the hippocampus.

Reminder treatments can also make remote memories that normally survive hippocampal lesions vulnerable to hippocampal damage (Debiec et al., 2002; Land, Bunsey, & Riccio, 2000). Land et al. (2000) trained rats to escape a footshock by moving to a lighted part of a Y-shaped apparatus (a signaled avoidance task). When rats were given a hippocampal lesion 30 days after training, performance on this task remained relatively intact, as it did in other studies (Kim & Fanselow, 1992). If a reminder of the context preceded the operation, however, hippocampal lesions after 30 days erased the fear memory. Memories thus remain vulnerable after reactivation long after they have ceased to be exclusively dependent on the hippocampus. Nevertheless, it is not the case that reconsolidation is entirely symmetric to acquisition. For example, the period of vulnerability of a memory is much shorter after

reconsolidation than after acquisition (Debiec et al., 2002; Nader, 2003).

The resulting picture is one that is difficult but not impossible to reconcile with consolidation theory. Memories are initially dependent on the hippocampus, become independent of it through consolidation, and then are returned to a hippocampus-dependent state through retrieval. If consolidated memories are stored in the neocortical traces, as suggested by models of consolidation (Alvarez & Squire, 1994; Meeter & Murre, 2004, in press), it is hard to see why this would be the case. Does retrieval of a consolidated memory destroy its neocortical base, requiring renewed consolidation to repair it? Are all memories destroyed and repaired after their retrieval? At present, this remains speculation, speculation that is, moreover, elicited by only a single study. A similar study investigating reconsolidation with inhibitory avoidance learning resulted in a more traditional Ribot curve of vulnerability: Fear memories were sensitive to protein synthesis inhibitors after a reminder only when reminder and injection took place within 14 days after learning (Milekic & Alberini, 2002). More studies are clearly needed to investigate the precise characteristics of reconsolidation. Thus, although its relevance for long-term memory consolidation is obvious, it is too early to know what lessons to take from it.

Alternatives

Although there are thus neuropsychological, functional imaging, and neuropharmacological studies (especially Bontempi et al., 1999; Izquierdo et al., 1997) that support consolidation theory, the main reason to suggest such a process remains the existence of the Ribot gradient in retrograde amnesia. Other explanations have also been offered for this gradient, however. The two most plausible candidates are the multiple trace theory of Nadel and Moscovitch (1997) and the semantization hypothesis.

Moscovitch and Nadel's Multiple Trace Model

From 1997 on, Nadel, Moscovitch, and colleagues (Moscovitch & Nadel, 1999; Nadel & Moscovitch, 1997; Nadel et al., 2000) have engaged in a concerted and coherent assault on consolidation theory. Most of their arguments against consolidation have already been mentioned, but they also have presented a competing view: multiple trace theory. Its central tenet is that the hippocampal complex, comprising the hippocampal formation and surrounding medial–temporal lobe neocortex, remains involved in the retrieval of all remote memories. Extensive medial–temporal lobe damage should therefore cause a flat retrograde amnesia with near complete loss of both recent and remote memories. Ribot gradients are, according to Nadel and Moscovitch (1997), found only with partial lesions of the hippocampal complex. To explain this, they hypothesize that memories in the hippocampus are replicated over time. Because remote memories have more copies in the hippocampus, they can survive greater levels of hippocampal damage. This idea forms the basis of simulation work with an analytical model as well as a connectionist one (Nadel et al., 2000). Both are only models of retrograde amnesia; multiple trace theory does not aim to explain anterograde amnesia or the relationship between anterograde and retrograde amnesia.

The computational implementations of the theory are not very convincing. In fact, the connectionist model is not wholly consistent with the theory. Moscovitch and Nadel (1999) stated that "the reactivated traces have minimal neural overlap in the medial temporal lobe, but extensive overlap in neocortex" (p. 89). In their description of the connectionist network, however, they remarked that "multiple replicated traces ascribed to one and the same memory highly overlap . . . and therefore produce a collective attractor, which may not coincide with any of the replicas" (Samsonovitch, Nadel, & Moscovitch, 1999, p. 7). This contradicts the minimal overlap that reactivated traces were said to have in the medial–temporal lobe and indeed must have for the theory to explain the Ribot gradient (if replicas of memories were strongly correlated, there would be no reason why larger lesions would spare memories with many replicas more often than memories with few replicas).

In the analytical model, Nadel et al. (2000) encountered a serious problem: Memories that were replicated often became so numerous that they dominated the entire memory store. This is a version of runaway consolidation encountered in simulations of consolidation (Meeter, 2003); memories that are consolidated have a higher likelihood of being consolidated anew and end up monopolizing consolidation resources. To deflect this problem, Nadel et al. (2000) proposed versions with either a limit to the number of copies any memory can collect or a limit on the time that a memory can be copied. Both changes seem a little ad hoc (Do memories come with tags specifying the amount of replication needed?), and neither change produces forgetting and Ribot curves that are particularly convincing (in both model variants, the oldest memories are best remembered, producing U-shaped forgetting curves).

If we concentrate on the verbal theory, it is not evident why multiple trace theory does not suffer from exactly the same flaws as consolidation theory. For example, the underlying process of trace replication is as unclear as that of consolidation. Does trace replication occur only with explicit rehearsal of memories? Is there an automatic process, operating perhaps during sleep, behind trace replication? Multiple trace theory also shares the greatest weakness of consolidation theory. Nadel and Moscovitch (1997) argued that the timing of consolidation is unconvincing: Why should such processes take 25 years, the duration of a medieval person's life? But why should trace replication take 25 years? Nadel et al. (2000) did propose a version in which the time that memories participate in trace replication is limited. In this version the Ribot gradient did not stretch very far, however, presumably only as far as trace replication occurred (see their Figure 2c).

We could imagine a variant of multiple trace theory that would not assume trace replication but instead a trace strengthening at each retrieval attempt, perhaps accompanied by a binding to a new context. The connectionist network could be seen as an implementation of such a process, and it could plausibly be equated with reconsolidation (reconsolidation would make no sense in the context of trace replication, as the creation of new copies of a memory should leave old copies alone). Although this equation would have the benefit of tying the theory to neurobiology, it would also force a reappraisal of what exactly the hippocampal complex of multiple trace theory is. In the studies of reconsolidation discussed earlier, it was the dorsal hippocampus in which protein synthesis was blocked (Debiec et al., 2002). If trace strengthening were to be

equated to reconsolidation, then multiple trace theory's hippocampal complex would have to be equated to the hippocampus and perhaps its immediate surroundings. This would make findings of graded retrograde amnesia after complete hippocampal lesions (Clark et al., 2002; Winocur et al., 2001) very problematic for the theory.

Although multiple trace theory thus has its flaws as an explanation of the Ribot gradient, there are undoubtedly data that it can explain better than consolidation theory. Most obviously, it can deal very well with patient data indicating a flat gradient in retrograde amnesia (e.g., Cipolotti et al., 2001) or an involvement of the hippocampus in the retrieval of remote episodic memories in functional brain imaging studies (Maguire et al., 2001; Ryan et al., 2001). Given the assumption that uncopied memories are lost from the hippocampus, it also deals well with the putative hippocampal NMDA receptor involvement in memory consolidation (Shimizu et al., 2000). However, data indicating a limited involvement of the hippocampus in retrieval of remote memories (Bontempi et al., 1999; Frankland et al., 2001; Haist et al., 2001; Niki & Luo, 2002) are problematic for multiple trace theory. Studies in which hippocampal deactivation is not complete, however, pose no challenge to the theory (Izquierdo et al., 1997). Moreover, if in semantic dementia patients there is a reverse gradient in retrograde amnesia and faster forgetting than in normal individuals, multiple trace theory would not be able to deal very well with that (Graham, 1999).

Semantization

As suggested in a previous section, some gradients in retrograde amnesia are open to the alternative explanation that the tested remote memories are qualitatively different from the tested recent memories. One such difference might be that the remote memories are semantic, whereas recent memories are episodic (Cermak, 1984). Episodic memories are generally seen as those bound to a spatial and temporal context (i.e., memories of events), whereas semantic memories are ones that contain our general knowledge of the world (Tulving, 1972, 1983). If semantic memory were spared in amnesia and episodic memory not spared, this would lead to an apparent loss of recent (episodic) memories with sparing of remote (semantic) memories.

In support of this explanation, it was noted that autobiographical incidents recalled by amnesic patients often come over more as semantic, inflexible stories than as episodic memories (Kinsbourne & Wood, 1975); they thus resemble general knowledge more than they do vivid memories of past events. However, several studies have shown that semantic memory is implicated in amnesia (Squire & Zola, 1998). There is, for example, little evidence that new learning of semantic memories can take place in the presence of dense episodic amnesia (Verfaellie, Koseff, & Alexander, 2000), whereas retrograde amnesia has been found even for the hallmark of semantic memory, lexical knowledge (Verfaellie, Reiss, & Roth, 1995). A sparing of semantic knowledge is thus probably untenable as an explanation for the Ribot gradient, at least if memories are thought of as rigidly divided into episodic and semantic memories.

Nevertheless, one might construct a theory of progressive "semantization" of memories with age to explain the Ribot gradient. In such a view, all memories start out as episodic, but with time some become semantic. This process can be thought of as one of decontextualization: Episodic memories are bound to a spatial and temporal context, and loss of this context information makes the memories semantic. Such a process is not far-fetched; in fact, it is a plausible theory of how semantic memories are formed (Schooler, Shiffrin, & Raaijmakers, 2001). The Ribot gradient can now be explained as the loss of recent, still episodic memories and the sparing of remote, semanticized memories. A hint of this "semantization" view of retrograde amnesia was already apparent in Cermak's (1984) report in which he described spared remote autobiographical memories as being part of "personal folklore." This theory was recently worked out in detail by Rosenbaum, Winocur, and Moscovitch (2001), though they framed their version in terms of different kinds of contexts.

Why would a lesion to the hippocampal system affect episodic memories more than semantic memories? There are two possibilities. First, episodic memories may be stored in the hippocampal system and semantic memories in the neocortex. This raises the question of how memories, in the process of semantization, are transported from the hippocampal system to the neocortex. Whatever the proposed mechanism, it will be difficult to distinguish from consolidation theory. Second, both kinds of memories may be stored in the neocortex, with only episodic memories needing the hippocampus for their retrieval. This is the possibility that Rosenbaum et al. (2001) seemed to have in mind, but it is not unproblematic. It raises the question of why memories need time to "semanticize," why semantic memories are not immediately spared by hippocampal lesions. According to Rosenbaum et al. (2001), memories may need to be repeated many times to build up representations strong enough to be retrieved without the help of the hippocampal system. If this were all, then semantization would come down to the idea that old memories survive hippocampal damage because they are overlearned and, through that overlearning, stored in the neocortex in a sufficiently strong, decontextualized way. This would be reminiscent of the "slow" and "fast" learning of semantic knowledge assumed by Holdstock et al. (2002) to explain findings from patients with childhood hippocampal lesions (Vargha-Khadem et al., 1997).

Most experiments showing Ribot gradients in experimental animals, however, have involved one-trial learning. Here overlearning cannot be the explanation for the Ribot gradient. Rosenbaum et al. (2001) did discuss such studies. Of one experiment involving socially acquired food preference, they stated that "with passage of time, the link between food preference and the relational context becomes less important than the memory for the preference itself" (Rosenbaum et al., 2001, p. 191). This gives the impression that episodic memories somehow fall apart, and what is left over is a semantic memory consisting of simple associations. Such an idea is consistent with findings from the animal conditioning literature, in which a loss of the context dependency of performance has been explained by assuming that animals forget contextual elements before forgetting more simple associations (Bouton, Nelson, & Rosas, 1999). However, links with context were purportedly stored in the hippocampal system. It is difficult to see how hippocampal forgetting might make neocortical semantic memories stronger.

It would seem, thus, that overlearning is the only tenable interpretation for the process of semantization. The idea that the neocortex stores simple associations that can be built up by multiple

repetitions is generally accepted (and is accepted by consolidation theorists; McClelland et al., 1995; Meeter & Murre, in press; Murre, 1997). Indeed, because consolidation theory also proposes that memories are stored in the neocortex via multiple learning trials, it would seem that semantization and consolidation are indistinguishable concepts. Two features separate them, though. Semantization has been presented as occurring because of explicit repetition and relearning (Rosenbaum et al., 2001), whereas consolidation is often thought of as an automatic process, perhaps occurring during sleep. Moreover, the semantization explanation is motivated by the idea that there are qualitative differences between memories retained and lost in amnesia (the latter are episodic in nature, the former not). Although consolidation theorists have generally not stated that a consolidated, neocortical memory is qualitatively indistinguishable from its forebearer that was bound together by the hippocampal system, they have certainly invited the suspicion that they think in such ways (i.e., by defending that remote, consolidated spatial memories of a patient with amnesia were indistinguishable from normal spatial memories; Teng & Squire, 1999).

Semantization is consistent with the episodic memory deficits seen in semantic dementia. If remote "episodic" memories are in fact semantic, the central tenet of semantization, then it is logical that those memories are lost when semantic memory is degraded. Studies showing a flat gradient in retrograde amnesia (Cipolotti et al., 2001) are also compatible with semantization if one assumes that they involved tests restricted to episodic memories. Some of the data indicating limited involvement of the hippocampus in retrieval of remote memories can be explained by assuming that episodic memories stored in the hippocampus are forgotten, whereas semantic memories stored in the neocortex are overlearned. This would lead to a shift, with time, of the brunt of retrieval from the hippocampus to the neocortex (Bontempi et al., 1999; Frankland et al., 2001; Haist et al., 2001; Niki & Luo, 2002). The danger with such explanations is, of course, that "semantic" and "episodic" become synonymous with "relying on the hippocampus" and "relying on the neocortex," which would make the theory unfalsifiable (episodic–semantic is one of those distinctions that become very fluid once one looks too closely; McKoon, Ratcliff, & Dell, 1986). Strict operationalization of "episodic" and "semantic" (or the two kinds of contexts that Rosenbaum et al., 2001, described and viewed as equivalent to the two kinds of memory) would be needed for semantization to be a useful theory of retrograde amnesia.

Despite its helpful vagueness, semantization cannot be reconciled with all studies. Animal studies showing graded retrograde amnesia after one-trial learning (e.g., Anagnostaras et al., 2001; Kim & Fanselow, 1992) must be rejected if semantization is the real explanation for the Ribot gradient. So must the study of Izquierdo et al. (1997), which pointed to a strengthening of cortical memories in the absence of overlearning. The findings of Debiec et al. (2002) concerning reconsolidation are also not intelligible if hippocampal and neocortical memories are seen as essentially independent. Moreover, retrograde amnesia for lexical knowledge (Verfaellie et al., 1995) remains a rather challenging finding for the theory: Would it be plausible to assume that even lexical knowledge starts its life as episodic memories?

Conclusion

Memory consolidation has often been invoked to explain the Ribot gradient in retrograde amnesia, the finding that after damage to the medial–temporal lobe, recent memories are affected more than remote memories. Despite more than a century of theorizing, the exact nature of such memory consolidation is still unclear. Computational models of consolidation have shed a little light on how it may be viewed, however. They have implemented consolidation as an automatic process in which neocortical memories are retrieved from a random cue through strong links to the hippocampus. Subsequently, connections within the hippocampal pattern are strengthened. From this implementation, several constraints on consolidation can be derived: There is a period in which memories are reactivated concurrently in the hippocampus and the neocortex. Then learning must take place in the neocortex, while plasticity in the hippocampus is low. Improvements in memory performance can be expected to follow from consolidation.

Consolidation is often thought to occur during sleep, and there is evidence that the just-mentioned conditions pertain during slow-wave sleep. Memories seem to be reactivated in both the hippocampus and the neocortex, neocortical reorganization takes place, plasticity is low in the hippocampus, and memory seems to improve somewhat through deep sleep. Two elements are still missing for this evidence to be conclusive. One is that during reactivation of memories in sleep, learning should be demonstrated in the neocortical sites where reactivations take place. The second element is that, whereas all evidence linking slow-wave sleep to memory was gathered in the first sleep episode after learning new material, consolidation must take place over much longer periods to be a viable explanation for the Ribot gradient. It is thus still speculative whether consolidation takes place during sleep. Even if it does, sleep would not necessarily be the only phase in which memory consolidation occurs.

Much of the appeal of consolidation theory has, for a long time, been that no other explanation for data from retrograde amnesia was satisfactory. The Ribot curve might be a methodological artifact. Although this possibility cannot be excluded, there is so far also no compelling evidence that it is the case. Two alternative explanations for the evidence are available. The central tenet of multiple trace theory is that the hippocampal memory system is crucial for the storage and retrieval of all episodic memories, independently of the age of the memory. Graded retrograde amnesia results, according to this theory, from partial damage to the hippocampus, which preferentially spares old memories that have been replicated often. Another explanation, here labeled semantization, assumes that all memories start out as episodic but that some become semantic through overlearning. After damage to the substrate of episodic memory (the hippocampus), these "semanticized" memories are spared, which explains the Ribot gradient.

All three theories—consolidation, multiple trace, and semantization—are to some extent speculative, and to many their differences may seem empirically intractable. Indeed, some studies offered here as evidence for consolidation have elsewhere been interpreted as evidence against it. Nevertheless, several empirical predictions differentiate the theories, and each deals better or

worse with some of the empirical data gathered so far (see Table 1 for a summary). In a strict sense, all three theories have already been falsified and can only be saved by either ad hoc additions or rejection of certain data. The most important inconsistencies are the following.

1. If the hippocampus is necessary for retrieval of memories independently of their age (as some fMRI studies indicate and can be derived from flat gradient studies), then consolidation theory must be rejected.

2. If total lesion or deactivation of the hippocampus leads to graded memory loss (e.g., Winocur et al., 2001), multiple trace theory is rejected. So it is when the hippocampus is less involved in the retrieval of remote episodic memories than of recent episodic memories (e.g., Bontempi et al., 1999).

3. If one-trial learning can lead to graded retrograde amnesia (e.g., Izquierdo et al., 1997), then semantization is rejected as an explanation for the Ribot gradient. The same is true when it can be established that there is no qualitative difference between memories retrained in graded retrograde amnesia and normal remote memories (e.g., as suggested by Teng & Squire, 1999).

More testable differences would probably come to light if the vagueness of all three theories were eliminated. Vaguest is perhaps semantization. The distinction between episodic and semantic memory is not always very clear (McKoon et al., 1986), but this vagueness is amplified substantially if individual memories change, during their lifetime, from episodic to semantic: One needs to assume an ill-defined process that transforms a memory from one ill-defined state to another. One way in which the distinction can again be sharpened is by specifying the role of context in storage and retrieval of both types of memory (Schooler et al., 2001). A first attempt in that direction has been made by Rosenbaum et al. (2001), with their distinction between associative and relational contexts.

Although the central mechanism of multiple trace theory is much clearer, the theory would be helped by a compelling computational implementation that shows the feasibility of its explanation of the Ribot gradient. Such an implementation would, it is hoped, also bring to the fore the consequences of the theory for memory function. Multiple trace theory, as well as consolidation theory, suffers from a lack of clarity about the process behind its central mechanism. Do consolidation and trace multiplication occur only during explicit retrieval of memories? Are they automatic processes occurring during sleep? Is reconsolidation the process behind multiple trace theory? Current vagueness allows even for a mushy compromise in which most consolidation occurs during conscious retrieval and consolidated memories are a little more semantic than unconsolidated ones. Some formulation according to these lines would probably be acceptable to proponents of all three theories, but that does not make it automatically correct.

An aspect on which all three theories are equally vague is the time course of the processes involved. Within consolidation theory, the results of Izquierdo et al. (1997) suggest a possible solution to this time problem. They imply that consolidation is perhaps best seen as a cascade wherein memories travel through several temporary depositories, with each depository functioning as the "link" for the next until a final region representation is established in the neocortex (e.g., from the hippocampus to the entorhinal cortex to the neocortex). The more stages destroyed, the longer the Ribot gradient may be.

Whether or not such a rephrasing of consolidation theory improves its ability to account for gradients, it is hoped that more research will soon enable the scientific community to choose among the three theories. Moreover, the moment at which consolidation during sleep can be proved or rejected seems near, and not

Table 1
Findings Discussed in This Article, Along With Explanations That the Three Discussed Theories Would Offer for Them

Finding	Consolidation	Multiple trace theory	Semantization
Graded RA after hipp. damage	Recent mem.: hipp.; remote mem.: neocortex	Partial hipp. damage	Recent mem.: episodic; remote mem.: semantic
Ungraded RA after hipp. damage	−	Total hipp. damage	Only episodic memory tested
Semantic RA (Verfaellie et al., 1995)	+	+	−
Semantic dementia	Reverse gradient, faster forgetting	No reverse gradient, no faster forgetting	Semantic: reverse gradient and faster forgetting; episodic: no gradient and normal forgetting
fMRI: more hipp. activity for recent mem. than remote	+	−	Remote memories semantic
fMRI: hipp. activity same for remote and recent	Hipp. activation during remote memory search unessential	+	All memories episodic
Izquierdo et al. (1997)	+	Hipp. deactivation not complete	−
Riedel et al. (1999)	+	Loss of all memories	Loss of all memories
Frankland et al. (2001)	+	−	+
Shimizu et al. (2000)	NMDA important for transmission	Information lost without trace copying	−

Note. RA = retrograde amnesia; hipp. = hippocampal; mem. = memories; + = unproblematic; − = inconsistent with the theory without ad hoc assumptions; fMRI = functional magnetic resonance imaging; NMDA = *N*-methyl-D-aspartate.

too early: One century of hypothetical memory consolidation is enough.

References

Albert, M. S., Butters, N., & Brandt, J. (1981). Patterns of remote memory in amnesic and demented patients. *Archives of Neurology, 38,* 495–500.

Albert, M. S., Butters, N., & Levin, J. (1979). Temporal gradients in the retrograde amnesia of patients with alcoholic Korsakoff's disease. *Archives of Neurology, 36,* 211–216.

Alvarez, R., & Squire, L. R. (1994). Memory consolidation and the medial temporal lobe: A simple network model. *Proceedings of the National Academy of Sciences, USA, 91,* 7041–7045.

Anagnostaras, S. G., Gale, G. D., & Fanselow, M. S. (2001). Hippocampus and contextual fear conditioning: Recent controversies and advances. *Hippocampus, 11,* 8–17.

Beatty, W. M., Salmon, D. P., Butters, N., Heindel, W. C., & Granholm, E. L. (1988). Retrograde amnesia in patients with Alzheimer's disease or Huntington's disease. *Neuropsychology of Aging, 9,* 181–186.

Berger, T. W., & Thompson, R. F. (1978). Neuronal plasticity in the limbic system during classical conditioning of the rabbit nictitating membrane response: I. The hippocampus. *Brain Research, 145,* 323–346.

Blagrove, M. (1991). A critical review of neural net theories of dream sleep. *Journal of Intelligent Systems, 1,* 227–257.

Bontempi, B., Laurent-Demir, C., Destrade, C., & Jaffard, R. (1999, August 12). Time-dependent reorganization of brain circuitry underlying long-term memory. *Nature, 400,* 671–675.

Bouton, M. E., Nelson, J. B., & Rosas, J. M. (1999). Stimulus generalization, context change, and forgetting. *Psychological Bulletin, 125,* 171–186.

Brown, A. S. (2002). Consolidation theory and retrograde amnesia in humans. *Psychonomic Bulletin & Review, 9,* 403–425.

Cermak, L. S. (1984). The episodic/semantic distinction in amnesia. In L. R. Squire & N. Butters (Eds.), *The neuropsychology of memory* (pp. 55–62). New York: Guilford Press.

Cipolotti, L., Shallice, T., Chan, D., Fox, N., Scahill, R., Harrison, G., et al. (2001). Long-term retrograde amnesia: The crucial role of the hippocampus. *Neuropsychologia, 39,* 151–172.

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.

Conway, M. A., Turk, D. J., Miller, S. L., Logan, J., Nebes, R. D., Cidis Meltzer, C., et al. (1999). A positron tomography (PET) study of autobiographical memory retrieval. *Memory, 7,* 679–702.

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

Dudai, Y., & Morris, R. (2000). To consolidate or not to consolidate: What are the questions? In J. Bolhuis (Ed.), *Brain, perception, memory: Advances in the cognitive sciences* (pp. 149–162). Oxford, England: Oxford University Press.

Ekstrand, B. R. (1967). Effect of sleep on memory. *Journal of Experimental Psychology, 75,* 64–72.

Fowler, M. J., Sullivan, M. J., & Ekstrand, B. R. (1973, January 19). Sleep and memory. *Science, 179,* 302–304.

Frank, M. G., Issa, N. P., & Stryker, M. P. (2001). Sleep enhances plasticity in the developing visual cortex. *Neuron, 30,* 1–20.

Frankland, P. W., O'Brien, C., Ohno, M., Kirkwood, A., & Silva, A. J. (2001, May 17). α-CaMKII-dependent plasticity in the cortex is required for permanent memory. *Nature, 411,* 309–313.

Galton, C. J., Patterson, K., Graham, K. S., Lambon Ralph, M. A., Williams, G., Antoun, N., et al. (2001). Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology, 57,* 216–225.

Graham, K. S. (1999). Semantic dementia: A challenge to the multiple-trace theory? *Trends in the Cognitive Sciences, 3,* 85–87.

Graham, K. S., Becker, J. T., & Hodges, J. R. (1997). On the relationship between knowledge and memory for pictures: Evidence from the study of patients with semantic dementia and Alzheimer's disease. *Journal of the International Neuropsychological Society, 3,* 534–544.

Graham, K. S., & Hodges, J. R. (1997). Differentiating the roles of the hippocampal complex and the neocortex in long-term memory storage: Evidence from the study of semantic dementia and Alzheimer's disease. *Neuropsychology, 11,* 77–89.

Graham, K. S., Patterson, K., Pratt, K. H., & Hodges, J. R. (1999). Relearning and subsequent forgetting of semantic category exemplars in a case of semantic dementia. *Neuropsychology, 13,* 359–380.

Graham, K. S., Simons, J. S., Pratt, K. H., Patterson, K., & Hodges, J. R. (2000). Insights from semantic dementia on the relationship between episodic and semantic memory. *Neuropsychologia, 38,* 313–324.

Haist, F., Bowden Gore, J., & Mao, H. (2001). Consolidation of human memory over decades revealed by functional magnetic resonance imaging. *Nature Neuroscience, 4,* 1139–1145.

Hasselmo, M. E. (1999). Neuromodulation: Acetylcholine and memory consolidation. *Trends in Cognitive Sciences, 3,* 351–359.

Hennevin, E., Hars, B., Maho, C., & Bloch, V. (1995). Processing of learning information in paradoxical sleep: Relevance for memory. *Behavioural Brain Research, 69,* 125–135.

Hodges, J. R., & Graham, K. S. (1998). A reversal of the temporal gradient for famous person knowledge in semantic dementia: Implications for the neural organisation of long-term memory. *Neuropsychologia, 36,* 803–825.

Holdstock, J. S., Mayes, A. R., Isaac, C. L., Gong, Q., & Roberts, N. (2002). Differential involvement of the hippocampus and temporal lobe cortices in rapid and slow learning of new semantic information. *Neuropsychologia, 40,* 748–768.

Izquierdo, I., Quillfeldt, J. A., Zanatti, M. S., Quevedo, J., Schaeffer, E., Schmitz, P. K., et al. (1997). Sequential role of hippocampus and amygdala, entorhinal cortex and parietal cortex in formation and retrieval of memory for inhibitory avoidance in rats. *European Journal of Neuroscience, 9,* 786–793.

Jenkins, J. G., & Dallenbach, K. M. (1924). Obliviscence during sleep and waking. *American Journal of Psychology, 35,* 605–612.

Jones Leonard, B., McNaughton, B. L., & Barnes, C. A. (1987). Suppression of hippocampal synaptic plasticity during slow-wave sleep. *Brain Research, 425,* 174–177.

Kapur, N. (1999). Syndromes of retrograde amnesia: A conceptual and empirical synthesis. *Psychological Bulletin, 125,* 800–825.

Karni, A., & Sagi, D. (1993, September 6). The time course of learning a visual skill. *Nature, 365,* 250–252.

Kim, J. J., & Fanselow, M. S. (1992, May 1). Modality-specific retrograde amnesia for fear. *Science, 256,* 675–677.

Kinsbourne, F. A., & Wood, D. (1975). Short-term memory processes and the amnesic syndrome. In D. Deutsch & J. A. Deutsch (Eds.), *Short-term memory* (pp. 257–291). New York: Academic Press.

Kopelman, M. D. (1989). Remote and autobiographical memory, temporal context memory, and frontal atrophy in Korsakoff and Alzheimer patients. *Neuropsychologia, 27,* 437–460.

Kopelman, M. D. (1994). The autobiographical memory interview in organic and psychogenic amnesia. *Memory, 2,* 211–235.

Kudrimonti, H. S., Barnes, C. A., & McNaughton, B. L. (1999). Reactivation of hippocampal cell assemblies: Effects of behavioral state, experience, and EEG dynamics. *Journal of Neuroscience, 19,* 4090–4101.

Land, C., Bunsey, M., & Riccio, D. C. (2000). Anomalous properties of hippocampal lesion-induced retrograde amnesia. *Psychobiology, 28,* 476–485.

Lechner, H. A., Squire, L. R., & Byrne, J. H. (1999). 100 years of

consolidation—Remembering Muller and Pilzecker. *Learning & Memory, 6,* 77–87.

Leplow, B., Dierks, C., Herrmann, P., Pieper, N., Annecke, R., & Ulm, G. (1997). Remote memory in Parkinson's disease and senile dementia. *Neuropsychologia, 35,* 547–557.

Levin, H. S., High, W. M., Jr., Meyers, C. A., Von Laufen, A., Hayden, M. E., & Eisenberg, H. M. (1985). Impairment of remote memory after closed head injury. *Journal of Neurology, Neurosurgery & Psychiatry, 48,* 556–563.

Louie, K., & Wilson, M. A. (2001). Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron, 29,* 145–156.

Lynch, S., & Yarnell, P. R. (1973). Retrograde amnesia: Delayed forgetting after concussion. *American Journal of Psychology, 86,* 643–645.

Maguire, E. A., Henson, R. N. A., Mummery, C. J., & Frith, C. D. (2001). Activity in the prefrontal cortex, not hippocampus, varies parametrically with the increasing remoteness of memories. *NeuroReport, 12,* 441–444.

Marr, D. (1971). Simple memory: A theory for archicortex. *Philosophical Transactions of the Royal Society of London, Series B, 262,* 23–81.

Mayes, A. R., Daum, L., Markowitch, H. J., & Sauter, B. (1997). The relationship between retrograde and anterograde amnesia in patients with typical global amnesia. *Cortex, 33,* 197–217.

McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. *Psychological Review, 102,* 419–457.

McGaugh, J. L. (2000, January 14). Memory—A century of consolidation. *Science, 287,* 248–251.

McGeoch, J. A. (1932). Forgetting and the law of disuse. *Psychological Review, 39,* 352–370.

McKoon, G., Ratcliff, R., & Dell, G. S. (1986). A critical evaluation of the semantic-episodic distinction. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 12,* 295–306.

Meeter, M. (2003). Control of consolidation in neural networks: Avoiding runaway effects. *Connection Science, 15,* 45–61.

Meeter, M., & Murre, J. M. J. (2004). Simulating episodic memory deficits in semantic dementia with the TraceLink model. *Memory, 12,* 272–287.

Meeter, M., & Murre, J. M. J. (in press). TraceLink: A connectionist model of consolidation and amnesia. *Cognitive Neuropsychology*.

Milekic, M. H., & Alberini, C. M. (2002). Temporally graded requirement for protein synthesis following memory reactivation. *Neuron, 36,* 521–525.

Milner, P. M. (1989). A cell assembly theory of hippocampal amnesia. *Neuropsychologia, 6,* 215–234.

Misanin, J. R., Miller, R. R., & Lewis, D. J. (1968, May 3). Retrograde amnesia produced by electroconvulsive shock after reactivation of consolidated memory trace. *Science, 160,* 554–555.

Moscovitch, M., & Nadel, L. (1999). Multiple-trace theory and semantic dementia: Response to K. S. Graham (1999). *Trends in the Cognitive Sciences, 3,* 87–89.

Moss, H. E., Kopelman, M. D., Cappelletti, M., de Mornay Davies, P., & Jaldow, E. (2003). Lost for words or loss of memories? Autobiographical memory in semantic dementia. *Cognitive Neuropsychology, 20,* 703–732.

Muller, G. E., & Pilzecker, A. (1900). Experimentelle Beitraege zur Lehre vom Gedaechtnis [Experimental contribution to the field of memory]. *Zeitschrift für Psychologie, Ergänzungsband, 1,* 1–300.

Muller Igaz, L., Vianna, M. R. M., Medina, J. H., & Izquierdo, I. (2002). Two time periods of hippocampal mRNA synthesis are required for memory consolidation of fear-motivated learning. *Journal of Neuroscience, 22,* 6781–6789.

Murray, E. A., & Bussey, T. J. (2001). Consolidation and the medial temporal lobe revisited: Methodological considerations. *Hippocampus, 11,* 1–7.

Murre, J. M. J. (1996). TraceLink: A model of amnesia and consolidation of memory. *Hippocampus, 6,* 675–684.

Murre, J. M. J. (1997). Implicit and explicit memory in amnesia: Some predictions by the TraceLink model. *Memory, 5,* 55–82.

Murre, J. M. J., Graham, K. S., & Hodges, J. R. (2001). Semantic dementia: Relevance to connectionist models of long-term memory. *Brain, 124,* 647–675.

Nadasdy, Z., Hirase, H., Czurko, A., Csicsvari, J., & Buzsaki, G. (1999). Replay and time compression of recurring spike sequences in the hippocampus. *Journal of Neuroscience, 19,* 9497–9507.

Nadel, L., & Bohbot, V. D. (2001). Consolidation of memory. *Hippocampus, 11,* 56–60.

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

Nadel, L., Samsonovitch, A., Ryan, L., & Moscovitch, M. (2000). Multiple trace theory of human memory: Computational, neuroimaging and neuropsychological results. *Hippocampus, 10,* 352–368.

Nader, K. (2003). Memory traces unbound. *Trends in Neuroscience, 26,* 65–72.

Nader, K., Schafe, G. E., & LeDoux, J. E. (2000, August 17). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature, 406,* 722–726.

Niki, K., & Luo, J. (2002). An fMRI study on the time-limited role of the medial temporal lobe in long-term topographical autobiographic memory. *Journal of Cognitive Neuroscience, 14,* 500–507.

Paller, K. A. (1997). Consolidating dispersed neocortical memories: The missing link in amnesia. In A. R. Mayes & J. J. Downes (Eds.), *Theories of organic amnesia* (pp. 73–88). Hove, England: Psychology Press.

Pavlides, C., & Winson, J. (1989). Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *Journal of Neuroscience, 9,* 2907–2918.

Philal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience, 9,* 534–547.

Phillips, W. A., & Silverstein, S. M. (2003). Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behavioral and Brain Sciences, 26,* 65–138.

Poe, G. R., Nitz, D. A., McNaughton, B. L., & Barnes, C. A. (2000). Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. *Brain Research, 855,* 176–180.

Qin, Y. L., McNaughton, B. L., Skaggs, W. E., & Barnes, C. A. (1997). Memory reprocessing in corticocortical and hippocampal neuronal ensembles. *Philosophical Transactions of the Royal Society of London, Series B, 352,* 1525–1533.

Reed, J. M., & Squire, L. R. (1998). Retrograde amnesia for facts and events: Findings from four new cases. *Journal of Neuroscience, 18,* 3943–3954.

Rempel-Clower, N. A., Zola, S. M., Squire, L. R., & Amaral, D. G. (1996). Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *Journal of Neuroscience, 16,* 5233–5255.

Ribot, T. (1881). *Les maladies de la memoire* [The diseases of memory]. Paris: Germer Baillare.

Riedel, G., Micheau, J., Lam, A. G. M., Roloff, E. V. L., Martin, S. J., Bridge, H., et al. (1999). Reversible neural inactivation reveals hippocampal participation in several memory processes. *Nature Neuroscience, 2,* 898–905.

Robins, A. V. (1995). Catastrophic forgetting, rehearsal, and pseudorehearsal. *Connection Science, 7,* 123–146.

Robins, A. V. (1996). Consolidation in neural networks and in the sleeping brain. *Connection Science, 8,* 259–275.

Robins, A. V., & McCallum, S. (1999). The consolidation of learning during sleep: Comparing the pseudorehearsal and unlearning accounts. *Neural Networks, 12,* 1191–1206.

Rosenbaum, R. S., Winocur, G., & Moscovitch, M. (2001). New views on old memories: Re-evaluating the role of the hippocampal complex. *Behavioural Brain Research, 127,* 183–197.

Russel, W. R., & Nathan, P. W. (1946). Traumatic amnesia. *Brain, 69,* 280–300.

Ryan, L., Nadel, L., Keil, K., Putnam, K., Schnyer, D., Trouard, T., et al. (2001). Hippocampal complex and retrieval of recent and very remote memories: Evidence from functional magnetic resonance imaging in neurologically intact people. *Hippocampus, 11,* 707–714.

Samsonovitch, A., Nadel, L., & Moscovitch, M. (1999, October). *Neural network model of multiple traces in hippocampus and retrograde amnesia.* Poster presented at the annual meeting of the Society for Neuroscience, Miami Beach, FL.

Schmaltz, L. W., & Theios, J. (1972). Acquisition and extinction of a classically conditioned response in hippocampectomized rabbits (*Oryctolagus cuniculus*). *Journal of Comparative and Physiological Psychology, 79,* 328–333.

Schmidtke, K., & Vollmer, H. (1997). Retrograde amnesia: A study of its relation to anterograde amnesia and semantic memory deficits. *Neuropsychologia, 35,* 505–518.

Schooler, L. J., Shiffrin, R. M., & Raaijmakers, J. G. W. (2001). A Bayesian model for implicit effects in perceptual identification. *Psychological Review, 108,* 257–272.

Shadmehr, R., & Holcomb, H. H. (1997, August 8). Neural correlates of motor memory consolidation. *Science, 277,* 821–825.

Shimizu, E., Tang, Y. P., Rampon, C., & Tsien, J. Z. (2000, March 9). NMDA receptor-dependent synaptic reinforcement as a crucial process for memory consolidation. *Science, 290,* 1170–1174.

Siegel, J. M. (2001, November 2). The REM sleep-memory consolidation hypothesis. *Science, 294,* 1058–1063.

Skaggs, W. E., & McNaughton, B. L. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep after spatial experience. *Journal of Neuroscience, 6,* 149–172.

Smith, C. (1996). Sleep states, memory processes and synaptic plasticity. *Behavioural Brain Research, 78,* 49–56.

Smith, C., & Lapp, L. (1991). Increases in number of REMS and REM density in humans following an intensive learning period. *Sleep, 14,* 325–330.

Snowden, J. S., Griffiths, H., & Neary, D. (1996). Semantic-episodic memory interactions in semantic dementia: Implications for retrograde memory function. *Cognitive Neuropsychology, 13,* 1101–1137.

Squire, L. R. (1992). Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review, 99,* 195–231.

Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: A neurobiological perspective. *Current Opinion in Neurobiology, 5,* 169–175.

Squire, L. R., Clark, R. E., & Knowlton, B. J. (2001). Retrograde amnesia. *Hippocampus, 11,* 50–55.

Squire, L. R., Cohen, N. J., & Nadel, L. (1984). The medial temporal region and memory consolidation: A new hypothesis. In H. Weingarter & E. Parker (Eds.), *Memory consolidation* (pp. 185–210). Hillsdale, NJ: Erlbaum.

Squire, L. R., Haist, F., & Shimamura, A. P. (1989). The neurology of memory: Quantitative assessment of retrograde amnesia in two groups of amnesic patients. *Journal of Neuroscience, 9,* 828–839.

Squire, L. R., & Slater, P. C. (1975). Forgetting in very long-term memory as assessed by an improved questionnaire technique. *Journal of Experimental Psychology: Human Learning and Memory, 1,* 50–54.

Squire, L. R., Slater, P. C., & Chace, P. M. (1975, January 10). Retrograde amnesia: Temporal gradient in very long-term memory following electroconvulsive therapy. *Science, 187,* 77–79.

Squire, L. R., & Zola, S. M. (1998). Episodic memory, semantic memory, and amnesia. *Hippocampus, 8,* 205–211.

Stickgold, R., Hobson, J. A., Fosse, R., & Fosse, M. (2001, November 2). Sleep, learning, and dreams: Off-line memory reprocessing. *Science, 294,* 1052–1057.

Stickgold, R., James, L., & Hobson, J. A. (2000). Visual discrimination learning requires sleep after training. *Nature Neuroscience, 3,* 1237–1238.

Sutherland, G. R., & McNaughton, B. L. (2000). Memory trace reactivation in hippocampal and neocortical neuronal ensembles. *Current Opinion in Neurobiology, 10,* 180–186.

Teng, E., & Squire, L. R. (1999, August 12). 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.

Tiunova, A. A., Anokhin, K. V., & Rose, S. P. R. (1998). Two critical periods of protein and glycoprotein synthesis in memory consolidation for visual categorization learning in chicks. *Learning and Memory, 4,* 401–410.

Tulving, E. (1972). Episodic and semantic memory. In E. Tulving & W. Donaldson (Eds.), *Organization of memory* (pp. 381–403). New York: Academic Press.

Tulving, E. (1983). *Elements of episodic memory*. Oxford, England: Clarendon Press.

Van Ormer, E. B. (1932). Retention after intervals of sleep and waking. *Archives of Psychology, 137,* 49.

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Paesschen, W. V., & Mishkin, M. (1997, July 18). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science, 277,* 376–390.

Verfaellie, M., Koseff, P., & Alexander, M. P. (2000). Acquisition of novel semantic information in amnesia: Effects of lesion location. *Neuropsychologia, 38,* 484–492.

Verfaellie, M., Reiss, L., & Roth, H. L. (1995). Knowledge of new English vocabulary in amnesia: An examination of premorbidly acquired semantic memory. *Journal of the International Neuropsychological Society, 1,* 443–453.

Vertes, R. P., & Eastman, K. E. (2000). The case against memory consolidation in REM sleep. *Behavioral and Brain Sciences, 23,* 867–876.

Westmacott, R., Leach, L., Freedman, M., & Moscovitch, M. (2001). Different patterns of autobiographical memory loss in semantic dementia and medial temporal lobe amnesia: A challenge to consolidation theory. *Neurocase, 7,* 37–55.

Whitty, C. W. M., & Zangwill, O. L. (1977). Traumatic amnesia. In C. W. M. Whitty & O. L. Zangwill (Eds.), *Amnesia* (pp. 118–135). London: Butterworths.

Williams, M., & Zangwill, O. L. (1952). Memory defects after head injury. *Journal of Neurology, Neurosurgery & Psychiatry, 15,* 54–58.

Wilson, M. A., & McNaughton, B. L. (1994, July 29). Reactivation of hippocampal ensemble memories during sleep. *Science, 255,* 676–679.

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

Wittenberg, G. M., & Tsien, J. Z. (2002). An emerging molecular and cellular framework for memory processing by the hippocampus. *Trends in Neuroscience, 25,* 501–505.

Zeelenberg, R., & Pecher, D. (2002). False memories and lexical decision: Even twelve primes do not cause long-term semantic priming. *Acta Psychologica, 109,* 269–284.

Zola-Morgan, S., & Squire, L. R. (1990, October 12). The primate hippocampal formation: Evidence for a time-limited role in memory storage. *Science, 250,* 288–290.

Received May 13, 2003
Revision received January 1, 2004
Accepted January 20, 2004 ■