

# Consolidation of long-term memory: Evidence and alternatives

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## Abstract

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 been presented, and have shown how consolidation can explain characteristics of amnesia, effects of arousal on memory, and episodic memory in semantic dementia. These models have not elucidated how consolidation must be envisaged; it remains a largely hypothetical process. Here findings are reviewed that shed light on how consolidation may be implemented in the brain. Moreover, evidence is weighed that supports its existence, or supports one of its competitors as explanations of the Ribot gradient: that it results from only partial damage to the hippocampal memory system (as stated by multiple trace theory), or that it result from a sparing of semanticized memories. Consolidation theory, multiple trace theory and semantization can all handle some findings well, and others not. Conclusive evidence for or against consolidation thus remains to be found.

## Consolidation of long-term memory: Evidence and alternatives

Consolidation, as a concept, has a century-old history (Lechner et al., 1999). It was originally proposed as an explanation for retroactive interference (Muller and 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 Psychlit in August 2003 on consolidation and memory, for example, received 1167 hits, of which more than a quarter were from the short period since 2000.

Consolidation is perhaps most often suggested as an explanation for the gradient in retrograde amnesia (Alvarez and Squire, 1994; McClelland et al., 1995; Murre, 1996). After damage to the hippocampal memory system, patients tend to lose more of their recent than of their remote memories (Kim and Fanselow, 1992; Kopelman, 1989; Squire, 1992). This pattern will here be referred to 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 and Alvarez, 1995; Squire et al., 1984). If the hippocampal system is damaged, recent memories are lost as they still depend on that system. Old memories have already been stored in the neocortex through consolidation, and are thus spared.

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 and Moscovitch, 1997; Nadel et al., 2000), consolidation theory has in the last years become controversial. Here, we will review what is known about consolidation, and what arguments have been forwarded for its existence. Finally, two alternative explanations for the Ribot gradient will be discussed and compared to 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 and 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 and Yarnell, 1973; Whitty and Zangwill, 1977). This immediate pre-onset 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 and Zangwill, 1952). The most likely explanation for immediate pre-onset 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 learning a visual skill, performance improved substantially following a delay of eight hours or more. They refer 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 and Holcomb, 1997). In the animal literature (e.g., Tiunova et al., 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 six hours after learning (Muller Igaz et al., 2002). This process of protein synthesis has been termed 'cellular consolidation' (Dudai and Morris, 2000).

Cellular consolidation or processes operating at even shorter time scales are not the consolidation that is invoked to explain the Ribot gradient. As 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 (it would also not be in agreement with the facts; 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 and Alvarez, 1995; Teyler and DiScenna, 1986; Wittenberg and Tsien, 2002), see Figure 2. This is also how extant models of memory consolidation have implemented the process (Alvarez and Squire, 1994; McClelland et al., 1995; Meeter, 2003; Meeter and Murre, 2003; Meeter and Murre, in press; Murre, 1996).

[Figure 1 about here](#)

[Figure 2 about here](#)

### Consolidation in connectionist models

The three models that have simulated cortico-hippocampal interactions (Alvarez and 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 from random cues (Alvarez and Squire, 1994; Meeter and Murre, 2003; Murre, 1996; Robins, 1996). Those patterns are then interleaved with new patterns to protect, repair or strengthen old ones. In TraceLink, for example (Meeter and Murre, 2003; Meeter and Murre, 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 letting the model, from an initial random state, 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, since consolidation in the TraceLink model is equivalent to additional learning. Experimental techniques should thus be able to find 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 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 and Squire, 1994; McClelland et al., 1995; Meeter and Murre, 2003; Murre, 1996). If during the reactivation learning occurs within the hippocampal system, runaway consolidation immediately rears its head, as now

consolidated memories become stronger in both the hippocampus and the neocortex (Meeter and Murre, 2003). Consolidation should therefore take place during a period that the hippocampus is not very plastic.

### **The 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 and Moscovitch, 1997): in no way does consolidation offer any constraints on how long the process might take. As will be 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. Since that length can vary from days or weeks in rats (Izquierdo et al., 1997; Kim and Fanselow, 1992; Winocur et al., 2001), via months in monkeys (Zola-Morgan and Squire, 1990) to years or decades in humans, consolidation may proceed faster in some species than in others (see McClelland et al., 1995, for estimates of the speed of consolidation derived from model-fitting). However, even within species the length of the Ribot curve can vary considerably (Murray and 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 et al., 1979; Mayes et al., 1997). Greater hippocampal system lesions may result in longer Ribot gradients (Nadel and Moscovitch, 1997), and its length probably varies with the age of the patient, the type of lesion, the 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 some more systematic estimates of the time course of consolidation and what it depends on.

Nadel and Moscovitch (1997) not only attacked 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 et al., 1988; Squire et al., 1989). A consolidation process lasting 25 years would, according to Nadel and Moscovitch (1997), stretch credulity, since 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 and Murre, 2003). 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 above, 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 et al., 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 and Bussey, 2001; Nadel and Moscovitch, 1997; Squire, 1992). Since 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 via processes that may also underlie semantic priming (i.e., the facilitation of one word through prior 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 and Pecher, 2002).

The most frequently proposed method of consolidation is rehearsal during sleep (Marr, 1971; McClelland et al., 1995; Robins and McCallum, 1999; Squire and 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. Increase in REM sleep intensity was observed in students after a period of examinations (Smith and 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 et al., 1995). Subsequent sleep also is characterized by a larger than usual biochemical activity connected to plasticity (Smith, 1996).

Psychological experiments have shown improvements of declarative memory after sleep (Ekstrand, 1967; Jenkins and Dallenbach, 1924; Van Ormer, 1932). Some studies have found slow-wave sleep to be helpful for declarative memory (Fowler et al., 1973; Philal and Born, 1997), others have found the effects to depend more on REM sleep (Smith, 1996). Striking improvements after sleep have been noted in simple skills (Stickgold et al., 2000). Critics have questioned whether REM sleep has a role in memory, however (Blagrove, 1991; Siegel, 2001; Vertes and Eastman, 2000): total elimination of REM sleep, as produced by a widely used class of antidepressants –MAO inhibitors– does not notably affect memory function in humans (Siegel, 2001). Other researchers have suggested that this may only be true for declarative memory, and that REM sleep is important for procedural learning (Stickgold et al., 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 and Alvarez, 1995), while at the same time plasticity is reduced in the hippocampus (Hasselmo, 1999; Jones Leonard et al., 1987). As was already discussed, this is what models of consolidation would require for its 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 et al., 1999; Pavlides and Winson, 1989; Skaggs and McNaughton, 1996; Sutherland and McNaughton, 2000; Wilson and McNaughton, 1994). Wilson and McNaughton (1994), for example, recorded hippocampal cells 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 and Wilson, 2001; Poe et al., 2000), and even in quiet waking – provided ripple activity was seen in the hippocampus (Kudrimonti et al., 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 cells with the same multielectrode devices as used by Wilson and McNaughton (1993). 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, while during sleep this situation may be reversed.

There is also evidence for cortical reorganization in sleep. In young cats, investigators covered one eye for six hours, 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 et al., 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 of consolidation 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 and McNaughton, 2000). No learning has, for example, been shown to take place during these reactivations. Moreover, reactivation has, until now, only been studied 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 last decade, however, support from other sources than neuropsychology has started to accumulate. We will 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 used human participants and one 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 versus that during retrieval of remote autobiographical memories, using functional MRI (fMRI). Both studies found hippocampal activation during retrieval to be unaffected by age of the memory (Maguire et al., 2001; Ryan et al., 2001), and one found 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 find evidence for a time-limited role of the hippocampus (Haist et al., 2001). In this study, people were shown faces of people of recent fame (who were famous in the '80s and '90s) and faces of people who had been famous in earlier decades ('40s to '70s). There was a small increase in right hippocampal complex activity with recent famous faces as compared to the remote famous faces. The fourth study, also using fMRI, investigated retrieval of memories for topographic locations (Niki and Luo, 2002). Places visited in the last one-and-a-half years were compared with places visited at least seven years ago. Recall of the more recent visits was associated with larger medial-temporal lobe activation as compared to the more remote visits, "peaking in the left parahippocampal gyrus" (Niki & Lou, 2002, p. 501). The fifth study, the only one to use PET, failed to find 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 studies discussed have drawbacks that make conclusions difficult. For example, memories used in the study were often elicited from the subjects in a session a few weeks (Maguire et al., 2001),

days (Niki and 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 and Luo, 2002; Ryan et al., 2001), and the task used by Maguire et al. (2001) may have been too undemanding (Niki and 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, while a null finding can always be a matter of a lack of power (indeed, with the public events questions used by Maguire et al. a small trend towards a greater activation of the hippocampus with recent memories was apparent). Moreover, there are 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, while 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 and Thompson, 1978), although the eyeblink conditioned response is actually acquired faster after hippocampal lesions (Schmaltz and Theios, 1972). Hippocampal activity during retrieval of remote memories might thus, as in the case of classical conditioning, reflect processing that is essentially superfluous for 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, as it is consistent with consolidation theory and not a trivial result).

Perhaps the strongest study showing such a pattern is the fifth using animals (Bontempi et al., 1999). Mice were trained on a radial arm maze discrimination problem, with a recall test occurring either five or twenty-five days after last training. Brain activity was measured after recall with help of a radioactive tracer. After the short interval, hippocampal activity was predominant, while after the long interval, no hippocampal activity was found (as compared to quiet controls). Instead, 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) offer as an alternative explanation for the results that retention interval was confounded with performance, and that 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, and the fact that performance was strongly correlated ( $r = .69$ ;  $p < 0.05$ ) with hippocampal activation after the short interval, but not at all after the long interval (instead, it correlated with frontal cortex and nucleus accumbens activations). 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 antagonist (LY326325). This was done either in the first seven 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, as 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 one day, 30 days or 60. 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 one-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 two months after learning the representation in the neocortex can sustain retrieval on its own.

Other evidence comes from a study (Frankland et al., 2001) in which wild-type mice were compared with mice that had a mutation resulting in severely impaired 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: though memories can be acquired via the hippocampus, they are forgotten more rapidly because of inadequate consolidation in the neocortex.

The three studies all seem to deliver strong support for consolidation theory. For two, however, alternative explanations are possible. In the case of the Riedel et al. (1999) study, five 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 the case that both the hippocampus and the neocortex store memories in a way sufficient for retrieval in the 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 hippocampus and neocortex. In other words, the 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, as it does not explain why at shorter intervals a lesion of 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 NMDA receptors in field CA1 of the hippocampus in the first four days after training. This led to a small loss in performance twelve days later. Performance was not affected by NMDA blockers delivered in the three days before the test, starting twelve days after training. Shimizu et al. (2000) saw their data as evidence for consolidation occurring within the hippocampus, instead of between the hippocampus and the neocortex. Consolidation theory as it has been modelled 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 and 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. Sceptics of consolidation have, for that reason, often been sceptic of the gradient as well. Nadel and Moscovitch (1997), for example, have claimed that ungraded memory loss is just as frequent as graded memory loss, and list a number of studies in which patients with

damage limited to the hippocampal region exhibited either flat retrograde amnesia or one 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 only be explained with an ad hoc assumption of undetected neocortical malfunctioning (Squire and Alvarez, 1995), inadequate sampling of memories, or a psychogenic component to the amnesia (as 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 et al., 2001; Brown, 2002; Kim and Fanselow, 1992; Kopelman, 1989; Rempel-Clower et al., 1996; Squire, 1992), and Nadel and Moscovitch (1997) also seem 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<sup>1</sup> (Meeter and Murre, 2003).

Patterns in the episodic memory of semantic dementia patients are also easy to understand in the light of consolidation theory (Graham, 1999; Meeter and Murre, in press; Murre et al., 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 et al., 1997; Snowden et al., 1996). This characteristic of semantic dementia was already 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 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 mechanisms would fall away.

Neuropsychological data is often noisy due to small sample sizes and considerable inter-patient 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 only possible in patients whose lesions are to a large extent limited to the hippocampal complex. Patients with such lesion of whom retrograde amnesia was assessed can be counted on perhaps three hands, and it is never the case that the rest of the brain is normal (Nadel and Moscovitch, 1997; Reed and Squire, 1998; Rempel-Clower et al., 1996).

Moreover, the 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 either be 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 on mean acquisition strength, memories are chosen in such way that it is a priori plausible that they were learned with the same strength. Examples are a test in which questions were asked about television series that had run

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<sup>1</sup> Consolidation theory predicts a correlation between impaired learning (anterograde amnesia) and loss of recent memories (graded retrograde amnesia), as both depend on the intactness of the hippocampal memory system. Empirically, the correlation tends to lie between 0.3 and 0.6 for patients with degenerative diseases or with mixed aetiology (Kopelman, 1989, 1991; Mayes et al., 1997; Schmidtke and 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 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 and Murre, 2003). Series of patients with damage limited to the hippocampus are too small to do meaningful correlational analyses on. However, when one orders the 8 patients reported by Squire and colleagues by the extent of retrograde amnesia, this ordering corresponds perfectly with that of both the extent of anterograde amnesia and of the size of the lesion (Reed and Squire, 1998; Rempel-Clower et al., 1996).

just one season (Squire and Slater, 1975), and one 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 just 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 given 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 have used 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 gradient 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 et al., 1981; Beatty et al., 1988; Leplow et al., 1997), and patients with semantic dementia show a reverse gradient (Graham and Hodges, 1997; Hodges and 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 et al., 1999; Moscovitch and Nadel, 1999). Moscovitch and Nadel (1999) have claimed that it does not: in their view, remote memories are not affected any more 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 items on the tests. These differences are, they claim, masked in the performance of normal controls by ceiling effects (Nadel et al., 2000).

Although not all tests of remote memory controls perform close to ceiling (e.g., incidents items of AMI; Graham and Hodges, 1997), two other developments have seriously undermined the consolidation story of semantic dementia. 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). Secondly, 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 levels close to that of patients with Alzheimer's disease when the perspective on the pictures is changed (Graham et al., 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 cueing, to the detriment of visual cueing of memories. This they support with observations from one patient with semantic dementia, who, with help of visual cues, could be made to remember his wartime memories of more than half a century ago (Nadel et al., 2000; also see Moss et al., 2003; Westmacott et al., 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 drawbacks of the human studies; experimenters have full control over the lesion size, and can precisely control how long before surgery they train animals on a task. Nevertheless, it is only in the last twenty years that animal work has started to weigh in on the retrograde amnesia discussion. Of around fifteen pertinent studies performed since then, a clear majority has found Ribot gradients (Murray and Bussey, 2001; Nadel and Bohbot, 2001; Squire et al., 2001). Some did not, and it is not yet clear what explains these conflicting results. Murray and Bussey (2001) list a number of

factors that may play a role, such as the use of a within subjects versus between subjects design (with within-subjects designs yielding more Ribot gradients, but being more open to alternative explanations), and the kind of lesion made (with more limited lesions favoring a Ribot gradient). However, also studies using a between-subjects design and a complete lesion of the hippocampus have demonstrated Ribot gradients (Clark et al., 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 that want to disqualify the Ribot gradient, although methodological confounds can not be wholly excluded.

### **Empirical challenges to the Ribot gradient**

Two recent findings have muddied the water, however, in both the human and the animal retrograde amnesia literature. One 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 all three had gained a substantial basis of general knowledge. The findings have led some to suggest that there are two ways of acquiring general knowledge, rapid, hippocampus-dependent learning, and slow, neocortical learning (Holdstock et al., 2002). This is not inconsistent with consolidation theory, as consolidation theorists have already assumed slow, implicit learning in the neocortex (Meeter and Murre, 2003). Others have argued against two ways of learning, suggesting that residual episodic memory is in all three cases enough to explain acquired knowledge (Squire and 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 (a phenomenon underlying graded amnesia after electroconvulsive therapy; Squire et al., 1975). It has long been known that older memories, normally immune to electroshocks, can become vulnerable again when they are retrieved just prior to the shocks (Misanin et al., 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 et al., 2000), and recently also to the hippocampus. Debiec et al. (2002) elicited contextual fear in rats by administering shocks in a distinct context. The test occurred four 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 vulnerable to hippocampal damage that normally survive hippocampal lesions (Debiec et al., 2002; Land et al., 2000). Land et al. (2000) trained rats to escape a footshock by moving to a lighted part of a Y-shaped apparatus (a signalled 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 and 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 and Squire, 1994; Meeter and Murre, 2003; Meeter and Murre, 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, one 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: the fear memories were only sensitive to protein synthesis inhibitors after a reminder when reminder and injection took place within fourteen days after learning (Milekic and Alberini, 2002). More studies are clearly needed to investigate the precise characteristics of reconsolidation. While its relevance for long-term memory consolidation is obvious, it is thus too early to know what lessons to take from it.

## Alternatives

Although there are thus neuropsychological, functional imaging and neuropharmacological studies (esp. 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 and Nadel, 1999; Nadel and Moscovitch, 1997; Nadel et al., 2000) have launched a concerted and coherent assault on consolidation theory. Most of their arguments against consolidation have already been mentioned above, but they also 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 the recent and remote memories. Ribot gradients are, according to Nadel and Moscovitch (1997), only found 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 and 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) state that "... the reactivated traces have minimal neural overlap in the medial temporal lobe, but extensive overlap in neocortex." (p. 89). In the description of the connectionist network, however, they remark 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." (Nadel et al., 2000). 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 whole 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 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 only occur 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). While 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 MTT is. In the studies of reconsolidation discussed earlier on, it is the dorsal hippocampus in which protein synthesis is blocked (Debiec et al., 2002). If trace strengthening would 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 is 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 and Luo, 2002) are problematic for Multiple Trace Theory. Studies where hippocampal deactivation was 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 normals, Multiple Trace Theory would not be able to deal very well with that (Graham, 1999).

## Semantization

As was already 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, while 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), while semantic memories are ones that contain our general knowledge of the world (Tulving, 1972; Tulving, 1983). If semantic memory were spared in amnesia and episodic memory not, 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 as more semantic, inflexible stories than as episodic memories (Kinsbourne and 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 and 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 et al., 2000), while retrograde amnesia has been found even for the hallmark of semantic memory, lexical knowledge (Verfaellie et al., 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 et al., 2001). The Ribot gradient can now be explained as the loss of recent, still episodic memories, and the sparing of remote, semantized memories. A hint of this ‘semantization’ view of retrograde amnesia was already apparent in Cermak’s (1984) paper, where he described spared remote autobiographical memories as being part of ‘personal folklore’. It was recently worked out in detail by Rosenbaum, Winocur and Moscovitch (2001), though they framed their version of this theory in terms of different kinds of context.

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, 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 is, 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) seem 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. Rosenbaum et al (2001) state that memories may need to be repeated many times to build up representations strong enough to be retrieved without 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, use one-trial learning. Here, overlearning cannot be the explanation for the Ribot gradient. Rosenbaum et al. (2001) do discuss such studies. Of one experiment involving socially acquired food preference, they state that “[w]ith 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, where a loss of context dependency of performance has been explained by assuming that animals forget contextual elements before forgetting more simple associations (Bouton et al., 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 semantization. The idea that the neocortex stores simple associations that can be built up by multiple repetitions is generally accepted, also by consolidation theorists (McClelland et al., 1995; Meeter and Murre, 2003; Murre, 1997). Indeed, as 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), while 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 forbearer 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 and Squire, 1999).

Semantization is consistent with 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 used tests restricted to episodic memories. Some of the data indicating a limited involvement of the hippocampus in retrieval of remote memories can be explained by assuming that episodic memories stored in the hippocampus are forgotten, while 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 and 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 et al., 1986). Strict operationalization of episodic and semantic (or the two kinds of context that Rosenbaum et al., 2001, describe and see 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 and Fanselow, 1992) must be rejected if semantization is the real explanation for the Ribot gradient. So does 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?

## Conclusions

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 over 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 via strong links to the hippocampus. Subsequently, connections within the hippocampal pattern are strengthened. From this implementation, several constraints on consolidation can be derived: that 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 above-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 the reactivations take place. The second element is that, while 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 given 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 are falsified, and must be saved by either ad hoc additions or rejection of certain data. The most important inconsistencies are the following:

- 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.
- If total lesion or deactivation of the hippocampus lead 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).
- 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 and Squire, 1999).

[Table 1 about here](#)

More testable differences would probably come to light if all three theories were ridden of their vagueness. 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 stab in that direction has been given by Rosenbaum et al. (2001), with their distinction between associative and relational context. 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 implementation would hopefully also bring clarity in 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 their central mechanism. Do consolidation or 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 even allows 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 those lines would probably be acceptable to proponents of all three theories, but that does not make it automatically right.

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 suggest that consolidation is perhaps best seen as a cascade, where 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 are 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 between the three theories. Moreover, the moment that consolidation during sleep can be proved or rejected seems near. Not too early: one century of hypothetical memory consolidation is enough.

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Table 1

Findings discussed in this paper, and explanations that the three discussed theories would offer for them. Hipp.=hippocampal; act.= activity; mem.=memories; r.a. = retrograde amnesia; + = unproblematic; - = inconsistent with the theory without ad hoc assumptions.

finding	consolidation	multiple trace theory	semantization
Graded r.a. after hipp. damage	recent mem.: hipp., remote mem.: neocortex	partial hipp. damage	recent mem.: episodic, remote mem.: semantic
Ungraded r.a. after hipp. damage	-	total hipp. damage	only episodic memory tested
Semantic r. a. (Verfaellie et al., 1995)	+	+	-
Semantic dementia	reverse gradient, faster forgetting	no reverse gradient, no faster forgetting	semantic: reverse gradient & faster forgetting, episodic: no gradient & normal forgetting
fMRI: more hipp. activity for recent mem. than remote	+	-	remote memories semantic
fMRI: hipp. activity same for remote & recent	hipp. activation during remote memory search unessential	+	all memories episodic
Izquierdo et al. (1997)	+	hipp. deactivation not complete	-
Riedel et al. (1997)	+	loss of all memories	loss of all memories
Frankland et al. (2001)	+	-	+
Shimizu et al. (2001)	NMDA important for transmission	information lost without trace copying	-

## Figure Caption

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) via 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 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.

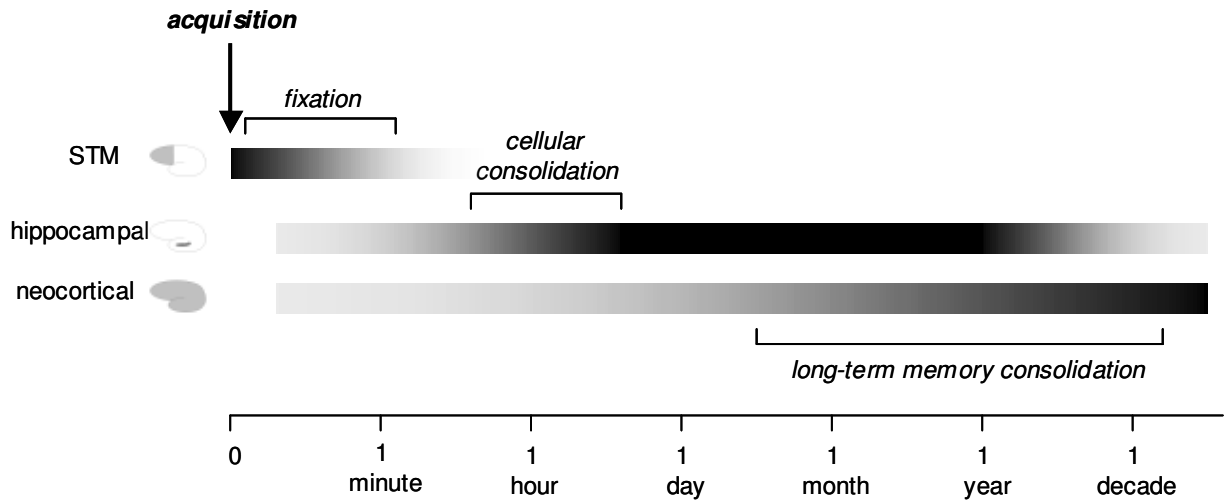


Figure 2: View of how consolidation contributes to memory, as incorporated in the TraceLink model (Meeter and Murre, 2003; Murre, 1996). TraceLink consists of three systems, neocortical memory repository (Trace system), a temporary medial temporal lobe memory store (Link system), and a system regulating the Link system's plasticity (Modulatory System). The normal formation of episodic memories is, for expository purposes, subdivided in four stages. *Stage 1:* A new memory representation activates a number of trace elements (shown as filled black 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.

