Amnesia/Review

In memory of consolidation

Susan J. Sara[1,3] and Bernard Hars[2]

[1]Centre Nationale de la Recherche Scientifique, Unité Mixte de Recherche (CNRS-UMR) 7152, Collège de France, Paris, France;
[2]CNRS-UMR 8620, University Paris 11, Orsay, France

How an animal learns, remembers, and uses information to guide adaptive behavior remains one of the most challenging questions in science today. Much progress was made in the twentieth century, and new tools available to neurobiological investigators have accelerated progress in the new century. Nevertheless, the road has been rocky and progress sometimes impeded by periodic polemic debates at a conceptual level. Retrospective examination of the nature of the divisive issues and how they were (or were not) resolved could help steer a new generation of investigators away from similar pitfalls and impasses. The same applies to scientists from other disciplines, recently joining in the "search for the engram," who might not be aware of the vast literature generated, mainly by psychologists, in the middle decades of the last century. Our purpose here is not to furnish a complete review of this literature, but to provide a historical perspective for some of the unresolved issues that continue to be discussed within the context of the field of neurobiology of memory. For more general reviews, refer to McGaugh (2000) and Dudai (2004).

Scientific investigation of memory processes was initiated at the end of the 19th century by psychologists in Germany, Ebbinghaus (1885) and then Müeller and Pilzecker (1900). Their studies of verbal learning and retention in human subjects led them to conclude that a memory trace was formed gradually over time after acquisition and they coined the term consolidation. Contemporary with this were the very influential clinical observations and theoretical elaborations of the French psychiatrist, Ribot (1882). From his studies of amnesic patients, he formulated "La loi de regression," which simply notes that, as memories age, they become more resistant to trauma-induced amnesia.

Consolidation and retrograde amnesia

The first animal model of amnesia is attributed to another psychologist, C.P. Duncan, who in 1945 published a paper entitled "The effect of electroshock convulsions on the maze habit in the white rat" (Duncan 1945). This was followed in 1948 by "Habit reversal deficit induced by electroshock in the rat" (Duncan 1948), culminating with "The retroactive effect of electroshock on learning" (Duncan 1949). In his first studies, Duncan administered an electroconvulsive shock (ECS) after each daily trial in a complex maze and showed an inverse relationship between the speed of learning and the delay between the trial and the amnestic treatment. In his 1949 paper he concluded that his experiments provided direct evidence for Müeller and Pilzecker's hypothesis stating that post-learning neural perseveration was necessary for consolidating memory. ECS disrupted this activity, thereby preventing post-acquisition memory consolidation. In the same year, and quite independently of Duncan's results, Hebb (1949) formalized this old idea that propagating or recurrent impulses of a specific spatio-temporal pattern underlie initial memory. This provided a strong rationale for the use of ECS as an amnesic agent to study the temporal dynamics of consolidation, since such a specific spatio-temporal pattern of neural activity could hardly be expected to survive the electrical storm induced by ECS. Thus the scientific study of memory became, for the most part, a study of function through dysfunction. Investigators overwhelmingly relied on amnesia, either clinical studies of amnesic patients or animal models of experimental amnesia. The protocol of retrograde amnesia, indeed, opened a door on a neurobiological approach to the study of memory, evaluating the efficacy and temporal dynamics of diverse physiological treatments without interfering with acquisition. In general, the rationale for these experiments was that treatments that disrupt ongoing brain activity (ECS, anesthesia, hypothermia) disturb memory. A large number of studies in the 1960s indicated that antibiotics that inhibited protein synthesis, injected before or immediately after learning, also lead to amnesia, expressed 24 h later (Flexner et al. 1963; Agranoff et al. 1965; Barondes and Cohen 1966, 1967). On the other side of the coin, treatments that enhance brain function such as psycho stimulant drugs (McGaugh 1966), or mild stimulation of the ascending reticular activation system (Bloch et al. 1966), facilitated memory consolidation. The common feature of these experiments is that both promnesic and amnesic agents lose their ability to respectively enhance or impair memory as the interval between memory acquisition and the treatment is increased, defining a temporal gradient of efficacy. This large body of data supported the consolidation hypothesis, which stipulates that (1) memories are fixated or consolidated over time, (2) once consolidated, memories are then stable, and (3) acquisition of a new memory and its consolidation together form a unique event; consolidation happens only once (McGaugh 1966, 2000).

Challenges to interpretation of amnesia as consolidation failure

Interestingly, prior and subsequent to these experimental amnesia studies, Duncan was interested in extinction phenomena, in particular, how reward magnitude and expectation influenced extinction. Much of this work was done in collaboration with D.J. Lewis, who later turned a critical eye on his mentor's work, to suggest initially, after careful behavioral analysis, that the performance deficit after ECS treatment was not necessarily due to amnesia, but to "competing responses" elicited by the treatment. In 1965, Lewis published a review of the ECS-induced amnesia literature, containing already at this early date over 40 references, concluding that they do not provide unequivocal support for the consolidation hypothesis. This early critical review rapidly raised a polemic public debate, the flavor of which can be gleaned from notes published in *Psychological Review* (Lewis and Maher 1965; McGaugh and Petrinovich 1965; Lewis and Maher 1966). Subsequent to this debate, scores of papers appeared from many different laboratories questioning the interpretation of experimental amnesia studies in terms of blockade of memory consolidation.

About the same time Weiskrantz (1966) suggested that human amnesia syndrome was not due to failure to consolidate but was due, at least in part, to retrieval dysfunction. He later published, with Elisabeth Warrington, the first evidence for perceptual priming effects in human amnesic subjects (although they did not refer to the procedure as priming at that time). Patients

[3]Corresponding author.
E-mail sjsara@ccr.jussieu.fr; fax 33-1-44273252.

and healthy controls learned lists of words and were tested several days later. Patients had marked deficits when tested for recall, and significant amnesia when tested under recognition conditions. However, when cued with a fragmented word, memory performance was no different from that of controls. For these clinical investigators, the fact that patients can express normal memory under certain test conditions suggested that the memory trace was intact, but could not be retrieved. They further proposed that all amnesia syndromes might be due to retrieval dysfunction (Warrington and Weiskrantz 1970; Weiskrantz and Warrington 1975). Quite independently, many investigators studying retrograde amnesia in animals were also suggesting that the phenomenon was due to inability to retrieve an intact memory at the time of testing, rather than to storage failure.

Recovery of memory

From his amnesia gradients, Duncan had estimated that consolidation required about one hour. It soon became clear, however, that the amnesia gradient did not give an indication of consolidation time, because of the wide variations in the slope of the gradient according to the amnesic agent used, the behavioral task, or simply the laboratory in which the study was carried out (Paolino et al. 1966; Gold et al. 1973; Gold and King 1974). Furthermore, many studies showed that ECS or other experimentally induced amnesias, like clinical retrograde amnesia, were often not permanent, but recovered spontaneously or after a reminder. Spontaneous recovery at various times after ECS-induced amnesia was reported by Cooper and Koppenaal (1964), D'Andrea and Kesner (1973), Kohlenberg and Trabasso (1968), and Young and Galluscio (1971). There were similar reports of spontaneous recovery after protein-synthesis induced amnesia as well (Quartermain et al. 1970; Serota 1971; Squire and Barondes 1972). Lewis, himself, contributed to this recovery literature showing that amnesia induced by ECS sometimes recovered spontaneously or could be reversed after "reminder" treatments (Lewis et al. 1968). This was later confirmed by many authors. Reminders before the retention test took the form of exposure to the CS, to the US (Koppenaal et al. 1967; Galluscio 1971; Miller and Springer 1972; Quartermain et al. 1972; Richardson et al. 1982), and to the training context (Quartermain et al. 1970; Sara 1973; Sara and David-Remacle 1974). A few investigators claimed that the reminder facilitated performance, not because it was a prompt for retrieval after an amnesic treatment, but because it provided a new learning opportunity (Cherkin 1972; Gold and King 1974).

ECS-induced amnesia could likewise be reversed by psychostimulant drugs such as strychnine (Gordon and Spear 1973; Sara and Remacle 1977) and amphetamine (Quartermain et al. 1988), or pituitary hormones (Rigter and Van Riezen 1979), given before the retention test. These pharmacological studies provided particularly strong arguments that the amnesic agent did not prevent formation of a memory trace. If the animal could express memory after a drug treatment, with no further exposures to the elements of the learning situation, then the recovery could hardly be attributed to new learning.

Thus there was a very large literature generated in the 60s and 70s that seriously challenged the interpretation of experimental amnesia studies in terms of prevention of memory consolidation. It seemed to be a logical imperative that, since memory could be expressed, consolidation must have taken place. There were a few reports of failure to reverse amnesia (Luttges and McGaugh 1967; Gold and King 1974), but the majority of studies showed that memory deficits in diverse behavioral tasks, induced by a wide range of amnesic agents, were either temporary or could be reversed by appropriate pre-test manipulations.

Cue–dependent amnesia

In parallel with the many studies clearly demonstrating recovery from experimental amnesia, there were several papers showing that a temporally graded retrograde amnesia could be obtained when the memory trace was reactivated just before the amnesic treatment. The first came from Lewis' group, showing that, when the rat received a reminder a day or two after avoidance training, memory was susceptible to ECS-induced amnesia, a phenomenon they called "cue-dependent amnesia" (Lewis and Maher 1965; Misanin et al. 1968; Lewis 1969). The phenomenon was later replicated by Mactutus et al. (1979), using hypothermia as the amnesic agent. Amnesia could likewise be induced by protein synthesis inhibition after a reminder, in much the same way that newly acquired memories are susceptible. Judge and Quartermain (1982) trained mice on a conditioned suppression task. Mice were injected with the protein synthesis inhibitor anisomycin at different time intervals after a single memory reactivation (exposure to the training context). There was a clear renewed efficacy of the treatment after reactivation, though the temporal gradient was steeper than for that generated after initial learning.

Active memories are not only subject to interference by amnestic agents, but can be facilitated by electrical stimulation of the reticular formation. Memory for a tone-shock association was reactivated by presentation of the tone in the learning context; four days after the initial learning a temporal gradient of treatment efficacy, similar to that seen after training, was obtained (Devietti et al. 1977).

Purely behavioral studies in animals and humans, carried out around the same period, also showed that retrieval induces memory lability. Gordon (1983), in a series of experiments in rats, showed that reactivation of memory by various reminders makes it vulnerable to interference by another task or to distortion by nonrelevant cues present at the moment of reactivation. These studies were compatible with the growing evidence from human studies suggesting that memory is substantially modified by incorporation of new information during retrieval (Loftus 1979, 1981). In the mind of all these authors, the modulation of long term memory is not an on-going continuous process, but occurs at transient windows of opportunity when the trace is in an active state. Reactivation can be spontaneous or trigged by external or internal events and, as discussed below, may even occur during sleep.

The concept of reconsolidation

In 1997, after twenty years of near eclipse, a serendipitous observation of a delayed amnesic effect of a drug on a well-trained spatial memory led to a rebirth of interest in cue-dependent amnesia in our laboratory. Recalling the reports of Lewis and others encouraged us to pursue a series of experiments examining amnesic effects of pharmacological intervention after a reactivation of different types of robust memory. Blockade of NMDA receptors induced a cue-dependent amnesia for a spatial discrimination task and for an odor-reward association task (Przybyslawski and Sara 1997; Torras-Garcia et al. 2005), while β receptor antagonists induced the same cue-dependent amnesia in those tasks as well as in an inhibitory avoidance task (Roullet and Sara 1998; Przybyslawski et al. 1999). We referred to the phenomenon as "reconsolidation," an unfortunate term that we would later regret, as a whole new field of "reconsolidation" emerged. Neither Lewis nor his contemporaries used the term reconsolidation and they were generally not interested in such questions as "does reconsolidation recapitulate consolidation?" Their aim had been merely to show that the amnesia gradient did not reflect the duration of a consolidation process and that consolidation was not a unique event. Memory was labile when in an active state, and lability was not time-bound to acquisition.

Reconsolidation studies continued with a study by Nader et al. (2000) showing that protein synthesis inhibition within the neural circuit involved in initial memory formation impairs memory after its reactivation. It is noteworthy that these experiments reintroduce the retrograde amnesia paradigm but, unlike earlier studies by David Quartermain, the amnesic agent is directed toward restricted targets in the brain involved in the initial consolidation. This report by Nader was soon followed by reports by many other laboratories showing cue-dependent amnesia, mostly involving aversive conditioning across a variety of vertebrate and invertebrate species. The great interest in this topic is reflected in the proliferation of studies. The current literature has been subject to extensive and continual review (Nader 2003; Dudai 2004; Alberini 2005; Alberini et al. 2006; Dudai 2006), so we will only outline the major issues here, especially when they bear an ironic resemblance to those earlier controversies surrounding consolidation.

Is post–reactivation amnesia permanent?

Some authors find that amnesia is as persistent after reactivation as after acquisition, while others find recovery from cue-dependent amnesia. When rats are submitted to a tone fear conditioning followed by anisomycin infusion in basal lateral amygdala (BLA), there is no spontaneous memory recovery, nor is recovery seen after a reminder (Duvarci and Nader 2004). On the other hand, in mice submitted to context fear conditioning and systemic injection of anisomycin, amnesia is durable after acquisition (21 d), but after reactivation it is necessary to use repeated injections and the amnesia is transitory: seen at one day but not at 21 d. (Lattal and Abel 2004; Prado-Alcala et al. 2006). Similar recovery after post-reactivation amnesia induced by anisomycin has been reported in chick (Anokhin et al. 2002)

Are the same structures and intracellular signaling pathways involved in acquisition and reactivation?

The neuroanatomical specificity of involvement during consolidation and reconsolidation is another question being addressed in reactivation studies. The BLA is involved in both consolidation and reconsolidation of tone fear conditioning in rat (Nader et al. 2000). Anisomycin infused in the hippocampus or the lesion of this structure 45 d after learning is able to induce amnesia if memory is reactivated (Nadel and Land 2000; Debiec et al. 2002). The insular cortex is involved in consolidation (Rosenblum et al. 1993) and in reconsolidation of a conditioned taste aversion (Eisenberg et al. 2003). In other paradigms, differences are observed. Anisomycin in the central amygdala blocks consolidation but not reconsolidation; in BLA it blocks extinction but not reconsolidation of conditioned taste aversion (Bahar et al. 2004).

Just as there is not yet a consensus concerning common neuroanatomical pathways in consolidation and reconsolidation, there is no clear picture concerning the intracellular signal pathways underlying post-learning and post-retrieval neural plasticity. Bozon et al. (2003) report activation of the transcription factor zif268 after both learning and retrieval of an object recognition task. On the other hand, in a conditioned fear memory, consolidation depends on hippocampal brain-derived neurotrophic factor (BDNF) but not the Zif268, whereas reconsolidation activates Zif268, but not BDNF in the hippocampus (Lee et al. 2004; for review, see Alberini et al. 2006).

Generality of reconsolidation

Since the current literature seems to be based almost exclusively on rodent fear conditioning, one might raise the question of the generality of cue-dependent amnesia. The initial reports did, however, use a very different type of learning positively reinforced discrimination in a linear maze (Lewis et al. 1972) or a radial arm maze (Przybyslawski and Sara 1997), and several recent studies use a variety of other tasks: conditioned taste aversion (Eisenberg et al. 2003; Gruest et al. 2004), object recognition (Kelly et al. 2003), inhibitory avoidance (Milekic and Alberini 2002), instrumental incentive learning (Wang et al. 2005), odor reward association (Torras-Garcia et al. 2005), and eyelid conditioning (Inda et al. 2005). A further argument for the generality of the phenomenon lies in the fact that reconsolidation is found not only in the rodent, but across species from humans (Walker et al. 2003) to invertebrates like crab (Frenkel et al. 2005), slug (Sangha et al. 2003; Gainutdinova et al. 2005), and honeybee (Stollhoff et al. 2005). Moreover, at least in the case of rodents, this aspect of memorization is already present at the beginning of life, showing that it is a fundamental aspect of memory (Gruest et al. 2004).

Boundaries on reconsolidation

The question remains whether every reactivation brings about reconsolidation. "Boundaries" to obtaining cue-dependent amnesia have been delimited by several investigators. For example, Eisenberg et al. (2003) showed that the strength of a memory trace can determine the outcome of a post-reactivation amnesic treatment. With a weak memory, resulting from a single training trial, unreinforced presentation of the CS results in extinction. If this is followed by an amnestic treatment, extinction is blocked and retention for initial learning is expressed at retention test. If the initial memory is strong, presentation of the CS reactivates the memory, rendering it labile, and amnesia is expressed at retention test.

Another way to shift from retrieval to extinction in behavioral control is to modify the duration or the repetition of the cueing episode: A brief retrieval will trigger a reactivation and so a reconsolidation process; a long or repeated retrieval will lead to extinction, i.e., new learning with its requirement for consolidation. Using a fear conditioning to context protocol, Suzuki et al. (2004) show that there is no amnesia with brief exposure to the CS (1 min), amnesia with a moderate exposure (3 min), and retention with a long CS exposure (30 min). This retention is interpreted as amnesia for the extinction induced by the 30-min unreinforced CS exposure. Interestingly they observe that the effective duration of cueing to induce a labile state increases with the strength or the age of the memory.

A further set of boundaries determining the extent to which cue-dependent amnesia can be obtained seems to concern the significance of the information. By significance of information is meant its predictive value or its association with reinforcement. Specifically, it has been shown that the memory of a familiar experimental context is not sensitive to amnesic treatment when reactivated, but, when fear conditioning has occurred in the same context, the contextual memory becomes labile and sensitive to amnesic treatments (Biedenkapp and Rudy 2004). So the significance of a stimulus may be added to the growing list of boundaries to reconsolidation.

A related determinant of the lability of a reactivated memory is the extent to which a new encoding mode is solicited at the time of retrieval (Morris et al. 2006). These authors show that a reactivated spatial reference memory, learned in the water maze over several days, is not susceptible to amnesia induced by injection of a protein synthesis inhibitor into the hippocampus. It is only when new information must be integrated into the existing memory that amnesia follows such injections. The results are in contrast to earlier reports of robust amnesia for a spatial reference memory task learned in the radial arm maze. This amnesia was obtained after reactivation of a well-trained spatial response followed by a single systemic treatment with an NMDA receptor antagonist (Przybyslawski and Sara 1997). There

are many differences between the two studies: The water maze is an aversive situation; the radial maze was rewarded with food; the amnestic agent in the former was protein synthesis inhibition in the hippocampus, in the latter systemically induced blockade of NMDA receptors. Nevertheless, this discrepancy is a caveat for the growing list of boundaries to reconsolidation. We have already discussed above the difficulty in drawing conclusions from negative outcomes of amnesia experiments. In the case of behavioral expression of amnesia, one has not proved that the trace has been erased or blocked. One is on even more tenuous grounds in claiming an absence of a reconsolidation process when there is behavioral retention after reactivation and amnesic treatment.

Reconsolidation: A "faux ami"

Why has reconsolidation attracted the attention of so many investigators? Currently an important part of neurobiological research on memory is an attempt to integrate molecular approaches (cf. Silva 2006). With the growing knowledge of functional genomics, neurobiologists are in a great hurry to apply increasingly sophisticated molecular tools to testing hypotheses concerning cellular mechanisms underlying plasticity and memory. What is needed are simple behavioral models and a straightforward conceptual framework. The consolidation hypothesis and experimental amnesia provide both. Moreover, viewing memory formation from within a consolidation-reconsolidation framework can accommodate some of the non-linear data generated by cellular and molecular investigations. But the term reconsolidation, under careful scrutiny, turns out to be a "faux ami."

Faux ami is the expression used in French to denote a word that, at first glance, is easily understood in another language because of its similarity but in reality has a different, sometimes even opposite, meaning or connotation. Reconsolidation, at face value, is a concept that is easily understood as an extension of the consolidation hypothesis. One of the reasons for this success, beyond the undeniable utility for explaining cue-dependent amnesia data, is its apparent simplicity. Everyone knows what consolidation means and hence can readily understand what reconsolidation denotes. Unfortunately, it is this faux ami that leads one to believe that the phenomenon of post-reactivation lability can be understood by a simple extension of the consolidation concept. The problem is that cue-dependent amnesia is not predicted by the consolidation hypothesis and is, in fact, in direct contradiction to it.

Retrieval and consolidation

In addition to several papers demonstrating cue-dependent amnesia, Donald Lewis published three important theoretical papers in which he thoroughly and thoughtfully reviewed the growing literature and argued for a cognitive interpretation of experimental amnesia (Lewis 1969, 1976, 1979). At the same time, many other critics were proposing that amnesia should be attributed to retrieval failure rather than information storage. Unfortunately, this view failed to inspire a new approach to the study of memory or provoke a significant change in paradigm. More influential were the theoretical elaborations of Endel Tulving (e.g., Tulving and Thomson 1973), who, along with Spear (1973, 1976) and Loftus (1979), held that memory consolidation cannot be considered independent of retrieval.

Beyond retrograde amnesia

The limits concerning the conclusions that can be drawn from any retrograde amnesia experiments are underlined when trying to compare the efficacy of amnestic treats when applied after training or after reactivation. If an animal expresses amnesia after training followed by amnestic treatment, one concludes that memory consolidation was blocked by the treatment. If the memory is subsequently expressed after a reminder or a pharmacological treatment, one must conclude that the trace was there, but for some reason the animal could not express it behaviorally. What about possible outcomes of experiments evaluating the putative reconsolidation processes? There the amnestic agent is applied after a reminder that is supposed to reactivate the memory. If a rat expresses amnesia on retention test, can it be taken as proof that the treatment erased or weakened the reactivated, labile trace by preventing reconsolidation? Suppose the memory is expressed at some later test? Or after a reminder? So here the problem of interpretation is no different from when the agent is applied after learning—we are faced with the impossible challenge of proving that the memory trace does not exist. When no cue-dependent amnesia is expressed on the retention test, there are several possible conclusions: (1) The amnestic agent was not effective in blocking reconsolidation (e.g., inappropriate dose), (2) the reactivation treatment was not sufficient to tap the target trace to put it into a labile state, or (3) reconsolidation is a myth.

Memory reactivation and consolidation during sleep

The notion that off-line memory processing occurs during sleep has been around for a long time. The waxing and waning of research interest in the topic parallels the interest in issues around memory consolidation in general. There was a surge of studies in the 60s and 70s followed by a quiescent period, then an apparently independent rekindling of interest in both clinical and animal studies in the last decade.

REM sleep was the focus of the early studies of sleep and memory, with the hypothesis that off-line memory consolidation occurred during this dream-associated phase of sleep. A large literature was generated showing that REM sleep deprivation, or its delayed onset after acquisition, impairs subsequent retention (Fishbein 1971; Hennevin and Leconte 1971; Greenberg and Pearlman 1974). In a complementary way, an increase in REM sleep occurs after a learning episode (Hennevin et al. 1974). Based on these observations, we proposed that the trace formed during wakefulness is reactivated during post-learning REM and is reprocessed. To test this hypothesis a promnesic treatment (mild stimulation of the mesencephalic reticular formation [MRF]) was administered during REM occurring after maze learning in rat. There was a marked improvement in performance compared with rats that received the MRF stimulation during slow wave sleep (SWS) or during wakefulness. That the effectiveness of the treatment is limited to REM sleep suggests that the new memory may become spontaneously active and labile during these episodes of sleep (Hennevin et al. 1989). In another experiment, memory was reactivated by presenting the CS at an intensity too weak to awaken the rat. The cue presented during REM facilitated performance on the following day, while there was no effect when it was given during wakefulness (Hars et al. 1985). Surprisingly, the cue had a disruptive effect when given during SWS (Hars and Hennevin 1987). Thus it seems that, when reactivation is triggered by a cue during the high level of brain activity of REM, there is a positive effect on memory reprocessing; when it is triggered during the low level of activity of SWS, memory is impaired. These two stages of sleep could have complementary roles in the selection of the relevant information for subsequent use, spontaneous reactivation in early SWS weakening nonpertinent information and subsequent reactivation during REM strengthening the residual significant memory (Hars 1988). Recent research has implicated REM sleep in memory formation in humans (Karni et al. 1994; Maquet 2000; Rauchs et al. 2004), in addition to the many studies showing the importance of SWS as

well (Gais et al. 2000, 2002). Some authors suggest that REM sleep is necessary for consolidation of procedural memories, while memories for declarative memories are processed during early SWS. Reactivation triggered by pertinent cues during different sleep stages has not yet been carried out in humans. Such studies could be of great interest in illuminating the complementary roles of REM and SWS to memory consolidation, as suggested by the rodent studies.

Electrophysiological studies in rat have suggested that circuits active during behavior are reactivated and replayed during subsequent sleep to promote memory consolidation. The emphasis has been on SWS (Wilson and McNaughton 1994; Skaggs and McNaughton 1996; Ribeiro et al. 2004), but a few studies have reported a similar phenomenon during REM sleep (Hennevin et al. 1998; Louie and Wilson 2001). A recent extensive review of the animal and human literature exploring the relationships between memory and sleep stages has emphasized the importance of taking into consideration the diversity of memory systems and the complexity of their interactions in trying to understand the role of sleep in memory consolidation (Rauchs et al. 2005). This might help to explain some of the discrepancies found in both the animal literature and human studies.

Imaging memory consolidation and retrieval

In vivo imaging techniques, ensemble electrophysiological recording, and ex vivo imaging of brain activity are promising methods to study memory processes from a more dynamic point of view. The group of Robert Jaffard was early pioneers in using ex vivo functional imaging methods in rodents to illustrate spatio-temporal dynamics of long term memory consolidation. Imaging labeled 2-deoxyglucose uptake, they showed widely distributed changes in brain metabolism after learning, depending on the level of learning and the time between behavioral session and sacrifice (Bontempi et al. 1996). Subsequent experiments revealed that the activation of a particular brain region at retrieval largely depended upon the age of the memory, with a progressive disengagement of hippocampus and increasing recruitment of cortical regions (Bontempi et al. 1999). These results clearly demonstrated a time-dependent reorganization of the neuronal circuitry underlying long-term memory storage, as suggested by earlier lesion studies. Further advances in delineating the temporal dynamics of specific molecular and cellular mechanisms involved in retrieval and consolidation of remote memories in specific cortical regions using ex vivo functional imaging techniques have been made recently and reviewed by Wiltgen et al. (2004).

It has been about a decade since functional Magnetic Resonance Imaging has been used to study brain correlates of cognition in human and nonhuman primates. The approach has already given us new insights and confirmed data from lesion and electrophysiological studies concerning brain regions implicated in encoding, consolidation, and retrieval of memories. Tulving was an early contributor to this, providing important new data regarding the respective roles of hippocampus and frontal regions in memory retrieval processes (Calabrese et al. 1996; Nyberg et al. 1996a,b). While these studies can provide information concerning memory-related spatio-temporal regional activation, they do not, at present, provide specific information concerning the local neural networks involved. There are continuous efforts to increase our understanding of the nature of the fMRI signal, by recording it simultaneously with the electrophysiological signal (e.g., Logothetis et al. 2001). This will inevitably increase still further the usefulness of this noninvasive technique in understanding the network dynamics of memory encoding, consolidation, and retrieval.

Conclusion and perspectives

Contemporary discussion concerning the nature of behavioral deficit in cue-dependent amnesia is disconcertingly reminiscent of the debate surrounding the consolidation question in the 1970s. These questions were never resolved with satisfaction and the conclusion of some investigators was that the paradigm, itself, was flawed in that experiments were designed to prove the nonexistence of a memory trace. The common sense of William James points to the fact that the way to study memory is through its retrieval, saying the only proof of there being retention is that recall takes place (James 1890). This seems a trivial statement, but consideration of the vast body of literature generated over the past century "in search of the engram" clearly indicates that this truism has not been given serious thought. The rapid development of functional imaging tools is opening new vistas for the scientific study of memory. This will hopefully lead to a change in the conceptual framework in which memory is viewed as a dynamic, open-ended process, with retrieval being an intricate part of the acquisition process. Retrieval occurs as a result of integration of incoming environmental information with the "memory network" driven by that information. It follows from this that retrieval will lead to the formation of new memories made upon the background of prior experience. Thus new memory cannot be acquired independently of retrieval of past experience, in that it is memory of the past which organizes and provides meaning to the present perceptual experience. Moreover, decoding or retrieval will change the information content of the "trace." In this view, every consolidation is, in fact, a "reconsolidation."

Acknowledgments

References

Agranoff, B.W., Davis, R.E., and Brink, J.J. 1965. Memory fixation in the goldfish. *Proc. Natl. Acad. Sci.* **54:** 788–793.

Alberini, C.M. 2005. Mechanisms of memory stabilization: Are consolidation and reconsolidation similar or distinct processes? *Trends Neurosci.* **28:** 51–56.

Alberini, C.M., Milekic, M.H., and Tronel, S. 2006. Memory: Mechanisms of memory stabilization and de-stabilization. *Cell. Mol. Life Sci.* **63:** 999–1008.

Anokhin, K.V., Tiunova, A.A., and Rose, S.P. 2002. Reminder effects-reconsolidation or retrieval deficit? Pharmacological dissection with protein synthesis inhibitors following reminder for a passive-avoidance task in young chicks. *Eur. J. Neurosci.* **15:** 1759–1765.

Bahar, A., Dorfman, N., and Dudai, Y. 2004. Amygdalar circuits required for either consolidation or extinction of taste aversion memory are not required for reconsolidation. *Eur. J. Neurosci.* **19:** 1115–1118.

Barondes, S.H. and Cohen, H.D. 1966. Puromycin effect upon successive phases of memory storage. *Science* **151:** 594–595.

———. 1967. Comparative effects of cycloheximide and puromycin on cerebral protein synthesis and consolidation of memory in mice. *Brain Res.* **4:** 44–51.

Biedenkapp, J.C. and Rudy, J.W. 2004. Context memories and reactivation: Constraints on the reconsolidation hypothesis. *Behav. Neurosci.* **118:** 956–964.

Bloch, V., Denti, A., and Hennevin, E. 1966. Effets de la stimulation réticulaire sur la phase de consolidation de la trace mnéique. *CR Acad Sc (Paris)* **266:** 384–387.

Bontempi, B., Jaffard, R., and Destrade, C. 1996. Differential temporal evolution of post-training changes in regional brain glucose metabolism induced by repeated spatial discrimination training in mice: Visualization of the memory consolidation process? *Eur. J. Neurosci.* **8:** 2348–2360.

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

Bozon, B., Davis, S., and Laroche, S. 2003. A requirement for the immediate early gene *zif268* in reconsolidation of recognition memory after retrieval. *Neuron* **40:** 695–701.

Calabrese, P., Markowitsch, H.J., Durwen, H.F., Widlitzek, H., Haupts, M., Holinka, B., and Gehlen, W. 1996. Right temporofrontal cortex as critical locus for the ecphory of old episodic memories. *J. Neurol. Neurosurg. Psychiatry* **61:** 304–310.

Cherkin, A. 1972. Retrograde amnesia in the chick: Resistance to the reminder effect. *Physiol. Behav.* **8:** 949–955.

Cooper, R.M. and Koppenaal, R.J. 1964. Suppression and recovery of a one-trial avoidance response after a single ECS. *Psychon. Sci.* **1:** 303–304.

D'Andrea, J. and Kesner, R. 1973. The effects of ECS and hypoxia on information retrieval. *Physiol. Behav.* **11:** 747–752.

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

Devietti, T.L., Conger, G.L., and Kirkpatrick, B.R. 1977. Comparison of the enhancement gradients of retention obtained with stimulation of the mesencephalic reticular formation after training or memory reactivation. *Physiol. Behav.* **19:** 549–554.

Dudai, Y. 2004. The neurobiology of consolidations, or, how stable is the engram? *Annu. Rev. Psychol.* **55:** 51–86.

———. 2006. Reconsolidation: The advantage of being refocused. *Curr. Opin. Neurobiol.* **16:** 174–178.

Duncan, C.P. 1945. The effect of electroshock convulsions on the maze habit in the white rat. *J. Exp. Psychol.* **35:** 267–278.

———. 1948. Habit reversal deficit induced by electroshock in the rat. *J. Comp. Physiol. Psychol.* **41:** 11–16.

———. 1949. The retroactive effect of electroshock on learning. *J. Comp. Physiol. Psychol.* **42:** 32–44.

Duvarci, S. and Nader, K. 2004. Characterization of fear memory reconsolidation. *J. Neurosci.* **24:** 9269–9275.

Ebbinghaus, H. 1885. *Uber das Gedachtnis: Untersuchungen zur experimentellen Psychologie.* Dunker & Humbolt, Berlin.

Eisenberg, M., Kobilo, T., Berman, D.E., and Dudai, Y. 2003. Stability of retrieved memory: Inverse correlation with trace dominance. *Science* **301:** 1102–1104.

Fishbein, W. 1971. Disruptive effects of rapid eye movement sleep deprivation on long-term memory. *Physiol. Behav.* **6:** 279–282.

Flexner, J.B., Flexner, L.B., and Stellar, E. 1963. Memory in mice as affected by intracerebral puromycin. *Science* **141:** 57–59.

Frenkel, L., Maldonado, H., and Delorenzi, A. 2005. Memory strengthening by a real-life episode during reconsolidation: An outcome of water deprivation via brain angiotensin II. *Eur. J. Neurosci.* **22:** 1757–1766.

Gainutdinova, T.H., Tagirova, R.R., Ismailova, A.I., Muranova, L.N., Samarova, E.I., Gainutdinov, K.L., and Balaban, P.M. 2005. Reconsolidation of a context long-term memory in the terrestrial snail requires protein synthesis. *Learn. Mem.* **12:** 620–625.

Gais, S., Plihal, W., Wagner, U., and Born, J. 2000. Early sleep triggers memory for early visual discrimination skills. *Nat. Neurosci.* **3:** 1335–1339.

Gais, S., Molle, M., Helms, K., and Born, J. 2002. Learning-dependent increases in sleep spindle density. *J. Neurosci.* **22:** 6830–6834.

Galluscio, E. 1971. Retrograde amnesia induced by electroconvulsive shock and carbon dioxyde anesthesia in rats: An attempt to stimulate recovery. *J. Comp. Physiol. Psychol.* **75:** 136–140.

Gold, P.E. and King, R.A. 1974. Retrograde amnesia: Storage failure versus retrieval failure. *Psychol. Rev.* **81:** 465–469.

Gold, P.E., Macri, J., and McGaugh, J. 1973. Retrograde amnesia gradients: Effects of direct cortical stimulation. *Science* **179:** 1343–1345.

Gordon, W.C. 1983. The malleability of memory in animals. In *Animal cognition and behavior* (ed. R.L. Mellgren), pp. 399–426. North Holland Press, Amsterdam.

Gordon, W.C. and Spear, N.E. 1973. The effects of strychnine on recently acquired and reactivated passive avoidance memories. *Physiol. Behav.* **10:** 1071–1075.

Greenberg, R. and Pearlman, C. 1974. Cutting the REM nerve: An approach to the adaptive role of REM sleep. *Perspect. Biol. Med.* **17:** 513–521.

Gruest, N., Richer, P., and Hars, B. 2004. Memory consolidation and reconsolidation in the rat pup require protein synthesis. *J. Neurosci.* **24:** 10488–10492.

Hars, B. 1988. *Reactivation de la trace mnéique et sommeil paradoxal: Éude chez l'animal.* Thèse Université de Paris-Sud, Centre d'Orsay, Orsay.

Hars, B. and Hennevin, E. 1987. Impairment of learning by cueing during postlearning slow-wave sleep in rats. *Neurosci. Lett.* **79:** 290–294.

Hars, B., Hennevin, E., and Pasques, P. 1985. Improvement of learning by cueing during postlearning paradoxical sleep. *Behav. Brain Res.* **18:** 241–250.

Hebb, D.O. 1949. *The organisation of behavior.* John Wiley, New York.

Hennevin, E. and Leconte, P. 1971. The function of paradoxical sleep: Facts and theories. *Annee Psychol.* **71:** 489–519.

Hennevin, E., Leconte, P., and Bloch, V. 1974. Paradoxical sleep increase triggered by learning, extinction and relearning of a response based on a positive reinforcement. *Brain Res.* **70:** 43–54.

Hennevin, E., Hars, B., and Bloch, V. 1989. Improvement of learning by mesencephalic reticular stimulation during postlearning paradoxical sleep. *Behav. Neural Biol.* **51:** 291–306.

Hennevin, E., Maho, C., and Hars, B. 1998. Neuronal plasticity induced by fear conditioning is expressed during paradoxical sleep: Evidence from simultaneous recording in the lateral amygdala and the medial geniculate in rats. *Behav. Neurosci.* **112:** 839–862.

Inda, M.C., Delgado-Garcia, J.M., and Carrion, A.M. 2005. Acquisition, consolidation, reconsolidation, and extinction of eyelid conditioning responses require de novo protein synthesis. *J. Neurosci.* **25:** 2070–2080.

James W. 1890. *The principles of psychology.* Holt, New York.

Judge, M.E. and Quartermain, D. 1982. Characteristics of retrograde amnesia following reactivation of memory in mice. *Physiol. Behav.* **28:** 585–590.

Karni, A., Tanne, D., Rubenstein, B.S., Askenasy, J.J.M., and Sagi, D. 1994. Dependence on REM sleep of overnight improvement of a perceptual skill. *Science* **265:** 679–682.

Kelly, A., Laroche, S., and Davis, S. 2003. Activation of mitogen-activated protein kinase/extracellular signal-regulated kinase in hippocampal circuitry is required for consolidation and reconsolidation of recognition memory. *J. Neurosci.* **23:** 5354–5360.

Kohlenberg, R. and Trabasso, T. 1968. Recovery of a conditioned emotional response after one or two electro-convulsive shocks. *J. Comp. Physiol. Psychol.* **65:** 270–273.

Koppenaal, R., Jogoda, E., and Cruce, J.A. 1967. Recovery from ECS produced amnesia following a reminder. *Psychon. Sci.* **9:** 293–294.

Lattal, K.M. and Abel, T. 2004. Behavioral impairments caused by injections of the protein synthesis inhibitor anisomycin after contextual retrieval reverse with time. *Proc. Natl. Acad. Sci.* **101:** 4667–4672.

Lee, J.L., Everitt, B.J., and Thomas, K.L. 2004. Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science* **304:** 839–843.

Lewis, D.J. 1969. Sources of experimental amnesia. *Psychol. Rev.* **76:** 461–472.

———. 1976. A cognitive approach to experimental amnesia. *Am. J. Psychol.* **89:** 51–80.

———. 1979. Psychobiology of active and inactive memory. *Psychol. Bull.* **86:** 1054–1083.

Lewis, D.J. and Maher, B.A. 1965. Neural consolidation and electroconvulsive shock. *Psychol. Rev.* **72:** 225–239.

———. 1966. Electroconvulsive shock and inhibition: Some problems considered. *Psychol. Rev.* **73:** 388–392.

Lewis, D.J., Misanin, J.R., and Miller, R.R. 1968. Recovery of memory following amnesia. *Nature* **220:** 704–705.

Lewis, D.J., Bregman, N.J., and Mahan Jr., J.J. 1972. Cue-dependent amnesia in rats. *J. Comp. Physiol. Psychol.* **81:** 243–247.

Loftus, E.F. 1979. The malleability of human memory. *Am. Sci.* **67:** 312–320.

———. 1981. Natural and unnatural cognition. *Cognition* **10:** 193–196.

Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., and Oeltermann, A. 2001. Neurophysiological investigation of the basis of the fMRI signal. *Nature* **412:** 150–157.

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

Luttges, M.W. and McGaugh, J.L. 1967. Permanence of retrograde amnesia produced by electroconvulsive shock. *Science* **156:** 408–410.

Mactutus, C.F., Riccio, D.C., and Ferek, J.M. 1979. Retrograde amnesia for old (reactivated) memory: Some anomalous characteristics. *Science* **204:** 1319–1320.

Maquet, P. 2000. Sleep on it! *Nat. Neurosci.* **3:** 1235–1236.

McGaugh, J.L. 1966. Time dependent processes in memory storage. *Science* **153:** 1351–1358.

———. 2000. Memory—A century of consolidation. *Science* **287:** 248–251.

McGaugh, J.L. and Petrinovich, L.F. 1965. Effects of drugs on learning and memory. *Int. Rev. Neurobiol.* **8:** 139–196.

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

Miller, R.R. and Springer, A.D. 1972. Induced recovery of memory in rats following electroconvulsive shock. *Physiol. Behav.* **8:** 645–651.

Misanin, J.R., Miller, R.R., and Lewis, D.J. 1968. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science* **160:** 554–555.

Morris, R.G., Inglis, J., Ainge, J.A., Olverman, H.J., Tulloch, J., Dudai, Y., and Kelly, P.A. 2006. Memory reconsolidation: Sensitivity of spatial memory to inhibition of protein synthesis in dorsal hippocampus

during encoding and retrieval. *Neuron* **50:** 479–489.

Müeller, G.E. and Pilzecker, A. 1900. Experimentalle beitrage zur lehre vom gedächtnis. *Z. Psychol.* **l:** 1–288.

Nadel, L. and Land, C. 2000. Memory traces revisited. *Nat. Rev. Neurosci.* **1:** 209–212.

Nader, K. 2003. Memory traces unbound. *Trends Neurosci.* **26:** 65–72.

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

Nyberg, L., McIntosh, A.R., Cabeza, R., Nilsson, L.G., Houle, S., Habib, R., and Tulving, E. 1996a. Network analysis of positron emission tomography regional cerebral blood flow data: Ensemble inhibition during episodic memory retrieval. *J. Neurosci.* **16:** 3753–3759.

Nyberg, L., McIntosh, A.R., Houle, S., Nilsson, L.G., and Tulving, E. 1996b. Activation of medial temporal structures during episodic memory retrieval. *Nature* **380:** 715–717.

Paolino, R.M., Quatermain, D., and Miller, N.E. 1966. Different temporal gradients of retrograde amnesia produced by carbon dioxide anesthesia and electroconvulsive shock. *J. Comp. Physiol. Psychol.* **62:** 270–274.

Prado-Alcala, R.A., Diaz Del Guante, M.A., Garin-Aguilar, M.E., Diaz-Trujillo, A., Quirarte, G.L., and McGaugh, J.L. 2006. Amygdala or hippocampus inactivation after retrieval induces temporary memory deficit. *Neurobiol. Learn. Mem.* **86:** 144–149.

Przybyslawski, J. and Sara, S.J. 1997. Reconsolidation of memory after its reactivation. *Behav. Brain Res.* **84:** 241–246.

Przybyslawski, J., Roullet, P., and Sara, S.J. 1999. Attenuation of emotional and nonemotional memories after their reactivation: Role of β adrenergic receptors. *J. Neurosci.* **19:** 6623–6628.

Quartermain, D., McEwen, B., and Azmita, E. 1970. Amnesia produced by electroconvulsive shock or cycloheximide: Conditions for recovery. *Science* **169:** 683–686.

———. 1972. Recovery of memory following amnesia in the rat and mouse. *J. Comp. Physiol. Psychol.* **79:** 360–379.

Quartermain, D., Judge, M.E., and Jung, H. 1988. Amphetamine enhances retrieval following diverse sources of forgetting. *Physiol. Behav.* **43:** 239–241.

Rauchs, G., Bertran, F., Guillery-Girard, B., Desgranges, B., Kerrouche, N., Denise, P., Foret, J., and Eustache, F. 2004. Consolidation of strictly episodic memories mainly requires rapid eye movement sleep. *Sleep* **27:** 395–401.

Rauchs, G., Desgranges, B., Foret, J., and Eustache, F. 2005. The relationships between memory systems and sleep stages. *J. Sleep Res.* **14:** 123–140.

Ribeiro, S., Gervasoni, D., Soares, E.S., Zhou, Y., Lin, S.C., Pantoja, J., Lavine, M., and Nicolelis, M.A. 2004. Long-lasting novelty-induced neuronal reverberation during slow-wave sleep in multiple forebrain areas. *PLoS Biol.* **2:** E24.

Ribot, T. 1882. *Diseases of memory*. Appleton-Century Crofts, New York.

Richardson, R., Riccio, D.C., and Mowrey, H. 1982. Retrograde amnesia for previously acquired pavlovian conditioning: UCS exposure as a reactivation treatment. *Physiol Psychol* **10:** 384–390.

Rigter, H. and Van Riezen, H. 1979. Pituitary hormones and amnesia. *Curr. Dev. Psychopharmacol.* **5:** 67–124.

Rosenblum, K., Meiri, N., and Dudai, Y. 1993. Taste memory: The role of protein synthesis in gustatory cortex. *Behav. Neural Biol.* **59:** 49–56.

Roullet, P. and Sara, S. 1998. Consolidation of memory after its reactivation: Involvement of β noradrenergic receptors in the late phase. *Neural Plast.* **6:** 63–68.

Sangha, S., Scheibenstock, A., and Lukowiak, K. 2003. Reconsolidation of a long-term memory in *Lymnaea* requires new protein and RNA synthesis and the soma of right pedal dorsal 1. *J. Neurosci.* **23:** 8034–8040.

Sara, S.J. 1973. Recovery from hypoxia and ECS-induced amnesia after a single exposure to training environment. *Physiol. Behav.* **10:** 85–89.

Sara, S.J. and David-Remacle, M. 1974. Recovery from electroconvulsive shock-induced amnesia by exposure to the training environment: Pharmacological enhancement by piracetam. *Psychopharmacology* **36:** 59–66.

Sara, S.J. and Remacle, J.F. 1977. Strychnine-induced passive avoidance facilitation after electroconvulsive shock or undertraining: A retrieval effect. *Behav. Biol.* **19:** 465–475.

Serota, R.G. 1971. Acetoxycycloheximide and transient amnesia in the rat. *Proc. Natl. Acad. Sci.* **68:** 1249–1250.

Silva, A.J. 2006. Consolidation: From dogma to historical note. In *Science of Memory: Concepts* (eds. H.R. Roediger et al.). Oxford University Press, Oxford, UK. (in press)

Skaggs, W. and McNaughton, B. 1996. Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science* **271:** 1870–1873.

Spear, N.E. 1973. Retrieval of memory in animals. *Psychol. Rev.* **80:** 163–194.

———. 1976. Retrieval of memories; a psychobiological approach. In *Handbook of learning and cognitive processes* (ed. W.K. Estes), Vol 4, pp. 17–90. Erlbaum, Hillsdale, N.J.

Squire, L.R. and Barondes, S.H. 1972. Variable decay of memory and its recovery in cycloheximide-treated rats. *Proc. Natl. Acad. Sci.* **69:** 1416–1420.

Stollhoff, N., Menzel, R., and Eisenhardt, D. 2005. Spontaneous recovery from extinction depends on the reconsolidation of the acquisition memory in an appetitive learning paradigm in the honeybee *Apis mellifera*. *J. Neurosci.* **25:** 4485–4492.

Suzuki, A., Josselyn, S.A., Frankland, P.W., Masushige, S., Silva, A.J., and Kida, S. 2004. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *J. Neurosci.* **24:** 4787–4795.

Torras-Garcia, M., Lelong, J., Tronel, S., and Sara, S.J. 2005. Reconsolidation after remembering an odor-reward association requires NMDA receptors. *Learn. Mem.* **12:** 18–22.

Tulving, E. and Thomson, D. 1973. Encoding specificity and retrieval processes in episodic memory. *Psychol. Rev.* **80:** 352–372.

Walker, M.P., Brakefield, T., Hobson, J.A., and Stickgold, R. 2003. Dissociable stages of human memory consolidation and reconsolidation. *Nature* **425:** 616–620.

Wang, S.H., Ostlund, S.B., Nader, K., and Balleine, B.W. 2005. Consolidation and reconsolidation of incentive learning in the amygdala. *J. Neurosci.* **25:** 830–835.

Warrington, E.K. and Weiskrantz, L. 1970. Amnesic syndrome: Consolidation or retrieval? *Nature* **228:** 628–630.

Weiskrantz, L. 1966. Experimental studies of amnesia. In *Amnesia* (eds. C. Whitty and O. Zangwill), pp. 1–31. Butterworth, London.

Weiskrantz, L. and Warrington, E.K. 1975. The problem of the amnestic syndrome in man and animals. In *The hippocampus* (eds. R.L. Isaacson and K.H. Pribram), Vol. 2, pp. 411–428. Plenum Publishing Corporation, New York.

Wilson, M. and McNaughton, B. 1994. Reactivation of hippocampal ensemble memories during sleep. *Science* **265:** 676–679.

Wiltgen, B.J., Brown, R.A., Talton, L.E., and Silva, A.J. 2004. New circuits for old memories: The role of the neocortex in consolidation. *Neuron* **44:** 101–108.

Young, A.G. and Galluscio, E.H. 1971. Recovery from ECS produced amnesia. *Psychon. Sci.* **22:** 149–151.

In memory of consolidation

Susan J. Sara and Bernard Hars

References	This article cites 111 articles, 32 of which can be accessed free at: **http://learnmem.cshlp.org/content/13/5/515.full.html#ref-list-1**
License	
Email Alerting Service	Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article or **click here.**