In memory of consolidation

Susan J. Sara1,3 and Bernard Hars2

1Centre Nationale de la Recherche Scientifique, Unité Mixte de Recherche (CNRS-UMR) 7152, Collège de France, Paris, France; 2CNRS-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 polemical 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 Müller 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 Müller 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 amnestic 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 fixed 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 polemical public debate, the flavor of which can be gleaned from notes published in Psychological Review (Lewis and Maher 1965; McGaugh and Petrovich 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...
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-Renacme 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 psycho-stimulant 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 hyperthermia 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 amnesic 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 (Lofthus 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 serendipitously observed delay 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 Quarteminier, 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 (Duvarc 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 (Przybylski 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 reacts 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 cuing 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 stimulus is more labile when reactivated, but, when fear conditioning has occurred in the experimental context is not sensitive to amnesic treatment when reactivated. Hence 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 (Przybylski 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 amnestic 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 nonlinear 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 (Rauch et al. 2005). This might help to explain some of the discrepancies found in both the animal literature and human studies.

### 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

We thank Yves Moricard for help in preparation of the manuscript and Oxana Yeshenko and Sophie Tronel for constructive comments.

### References


