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THE NEUROBIOLOGY OF CONSOLIDATIONS, OR, HOW STABLE IS THE ENGRAM?

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■ **Abstract** Consolidation is the progressive postacquisition stabilization of long-term memory. The term is commonly used to refer to two types of processes: synaptic consolidation, which is accomplished within the first minutes to hours after learning and occurs in all memory systems studied so far; and system consolidation, which takes much longer, and in which memories that are initially dependent upon the hippocampus undergo reorganization and may become hippocampal-independent. The textbook account of consolidation is that for any item in memory, consolidation starts and ends just once. Recently, a heated debate has been revitalized on whether this is indeed the case, or, alternatively, whether memories become labile and must undergo some form of renewed consolidation every time they are activated. This debate focuses attention on fundamental issues concerning the nature of the memory trace, its maturation, persistence, retrievability, and modifiability.

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INTRODUCTION

In the domain of memory research and theory, consolidation (Latin for "to make firm"), or memory consolidation, refers to the progressive postacquisition stabilization of long-term memory, as well as to the memory phase(s) during which such presumed stabilization takes place (Dudai 2002a). It has long been suggested that fresh memories need time to stabilize, and that often, such traces are prone to interference by distracting stimuli, injuries, or toxins, which, however, lose their effectiveness with the passage of time. The first documented reference to memory consolidation is in the writings of Quintillian, the noted Roman teacher of rhetoric, who turns his readers' attention to the "curious fact . . . that the interval of a single night will greatly increase the strength of the memory," and raises the possibility that " . . . the power of recollection . . . undergoes a process of ripening and maturing during the time which intervenes" (Quintillian first century A.D.). That such posttraining, time-dependent maturation process takes place was therefore probably known in the Middle Ages to orators and mnemonists who were well versed in the writings and mnemonotechniques of their Roman predecessors. The idea resurfaced again occasionally in different versions before the birth of experimental psychology (e.g., Hartley 1810).

The term "consolidation" is attributed to Muller & Pilzecker, who rediscovered, in a series of studies carried out in Gottingen between 1892 and 1900, that memory takes time to fixate, or undergo *Konsolidierung* (Muller & Pilzecker 1900). Their evidence was based on systematic search for the laws that govern the acquisition and retrieval of verbal material, á la Ebbinghaus (1885). Muller & Pilzecker found that correct recall of the target material improved during the first few minutes after training, and that if presented during the first minutes after training, intervening new stimuli tend to impair recall of the target material (a phenomenon they termed "retroactive inhibition"). They suggested that this reflects a posttraining interval during which associations consolidate in memory. Interestingly, as aptly noted by Lechner et al. (1999), though the Muller & Pilzecker study is frequently cited and referred to as the beginning of the modern era in the prolific field of memory consolidation, it has never been translated in full from German, and non-German readers must rely on abstracts and extracts (Lechner et al. 1999,

McDougall 1901). In spite of several reports of failure to replicate the aforementioned Muller & Pilzecker's findings (e.g., McGeoch 1933, reviewed and analyzed in Wixted 2004), their conclusion, that the trace is still uncompleted when training is over, has been overall well consolidated in the collective memory of memory research.

Shortly before Muller & Pilzecker introduced the term, the process of consolidation was also proposed based on clinical data. In "global," organic amnesia, memory of the recent past is commonly affected more than memory of the distant past; this observation is epitomized in Ribot's Law, or the Law of Regression: "Progressive destruction advances progressively from the unstable to the stable" (Ribot 1882). The idea was further elaborated a few years later by Burnham, who in a signal paper on amnesia integrated findings from experimental psychology and neurology, while at the same time emphasizing the dynamic nature of postexperience memory maturation: "There must be time for the processes of organization and assimilation (of memory) to take place. There must be time for nature to do her part. . .. Hurry defeats its own end" (Burnham 1903). It is noteworthy that Burnham's "time" actually refers to two different types of consolidation kinetics: fast, such as unveiled by the studies of Muller & Pilzecker, and slow, such as unveiled by the observations of residual premorbid memory in global amnesics. This temporal dichotomy suggests at the outset that the generic term "consolidation" conceals different types of processes and mechanisms. This is reflected in the title of this chapter and is further discussed below.

The quest for the neurobiological foundations of both slow and fast consolidation gained real momentum only in the second half of the last century. Quantitative, systematic studies of retrograde amnesia started to appear in the 1960s and 1970s (e.g., Sanders & Warrington 1971). These were accompanied by the development of animal models of human amnesia and attempts to identify brain substrates critical for slow consolidation (reviewed in Squire et al. 2001). In parallel, neuropharmacology, first systemic and later targeted to selected brain areas, began to unravel molecular candidates for the cellular machinery that subserves fast consolidation (Dudai & Morris 2000; McGaugh 1966, 2000). Cellular preparations and advanced molecular biology and neurogenetics have together revolutionized the field in the past two decades (Dudai 2002a, Milner et al. 1998). For the first time since Quintillian noted it, Ribot conceptualized it, and Muller & Pilzecker named it, we are now in a position to discuss the processes and mechanisms of consolidation at multiple levels of brain organization, from the molecular to the behavioral. Furthermore, the time is now ripe to reevaluate the status of the consolidation hypothesis: How valid is it? And what are the implications concerning the stability and retrievability of engrams and the nature of memory? In this review, I first discuss two main types of neuronal processes to which the term "consolidation" currently refers; then review data that have recently stirred anew a heated debate concerning the nature of the consolidated trace, and discuss their possible interpretation; and finally focus on selected issues that bear on our understanding of the nature of the engram and its persistence.

ON THE TERMINOLOGY OF CONSOLIDATION

The term "consolidation" is currently used in the neuroscience literature to refer to two types of processes, or a family of processes (Dudai 1996, Dudai & Morris 2000; Figure 1). One type is accomplished within the first minutes to hours after the encoding has occurred or practice ended. Ample evidence indicates that this relatively fast type of process takes place in local nodes in the neuronal

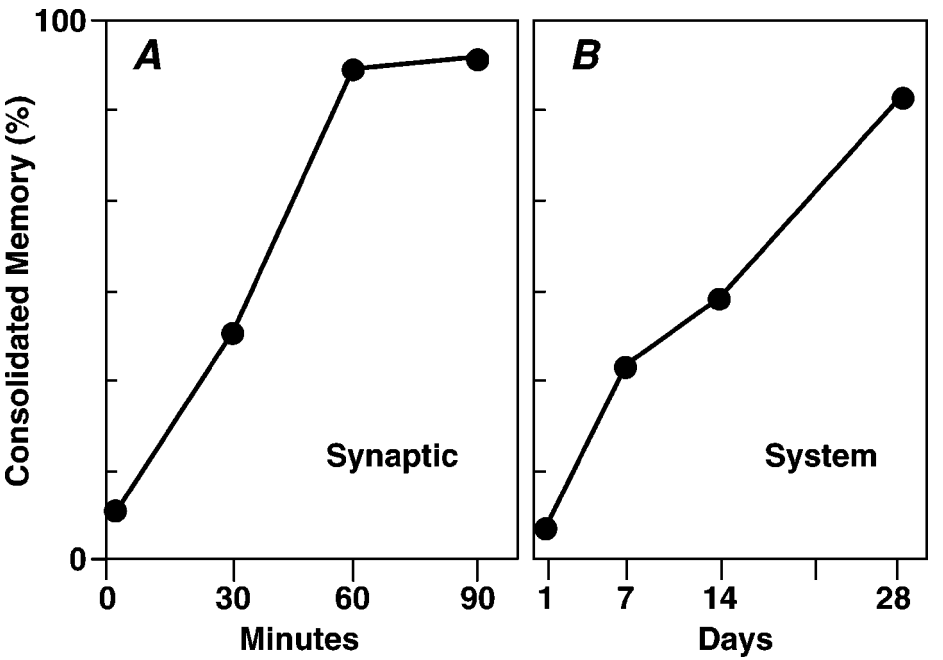


Figure 1 Types of consolidation. (*A*) The time course of *synaptic* (cellular, local) consolidation, determined by measuring the sensitivity of memory to the inhibition of protein synthesis. Consolidated memory is defined as treatment-resistant long-term memory. The data are from experiments on shuttle-box learning in the goldfish (Agranoff et al. 1966). The protein synthesis inhibitor was administered to separate groups of fish at the indicated time points after training. The sensitivity of memory to protein synthesis inhibition was over by about one hour. A consolidation process that depends on protein synthesis during and immediately after training is a universal property of the nervous system. (*B*) The time course of *system* consolidation, determined by measuring the sensitivity of long-term memory to hippocampal damage. The data are from experiments on contextual fear conditioning in the rat (Kim & Fanselow 1992). The lesion was inflicted to separate groups at the indicated time points after training. The dependence of long-term memory on the hippocampus in this case was over by about one month. System consolidation, lasting weeks or longer, during which the memory becomes independent of the hippocampus, is observed in declarative memory. (Figure adapted from Dudai 2002a.)

circuit(s) that encode(s) the experience-dependent internal representation, i.e., the memory. Much attention has been devoted to processes and mechanisms of fast consolidation in synapses; therefore the phenomenon is commonly termed "synaptic consolidation." But it is now evident that this type of consolidation depends on cross talk between synapses and their cell body and nucleus (Dudai & Morris 2000, and see below). The terms "cellular" or "local consolidation" are therefore also appropriate. "Synaptic consolidation" will be preferred in the current discussion, because it focuses on a major site of use-dependent modification in neuronal circuits, and fits the prevailing dogma that synaptic plasticity underlies learning and memory.

Another type of consolidation process(es) takes weeks, months, or even years to be accomplished. It is believed to involve reorganization over time of the brain circuits, or the systems, that encode the memory, and in the course of this the trace may spread to new locations in the brain while at the same time relinquishing its dependence on parts of the circuits that have subserved its acquisition. This type of process is termed "system consolidation." The term "reorganization" has been proposed, but brain reorganization may occur under conditions other than memory consolidation, such as development, housekeeping, and homeostasis, and response to injury—though similar neural mechanisms might be involved. Moreover, shifting levels of analysis, reorganization applies to synaptic consolidation as well, involving remodeling of synaptic connectivity. "Slow consolidation" is sometimes used to refer to system consolidation, but is questionable because there might be cases in which system consolidation is accomplished within a time frame not so different from that of synaptic consolidation. "Early" and "late" consolidation is also occasionally used, which is fine as far as no implicit assumption is being made about when the process starts. And last, the terms "short-term" and "long-term" consolidation are also used to refer to synaptic and system consolidation, respectively, but this should be better avoided because these terms may connote short or long persistence of the trace, which is a different issue.

GENERIC CRITERIA FOR CONSOLIDATION

Because the assumption that some form or another of consolidation does take place has already attained the status of tenet in the neurobiology of memory (admittedly, with lingering opposition, as noted below), it is prudent to review the criteria for demonstrating that consolidation has indeed taken place in a given system or preparation. By definition, consolidation is progressive postacquisition stabilization of memory. Hence to demonstrate consolidation, a limited time window of susceptibility of long-term memory to an amnesic agent must be proven, following cessation of experience or training. This agent should be devoid of significant effects on sensorimotor faculties required to execute the task, as well as on acquisition per se and on short-term memory, and should not induce state-dependent memory in the protocol used. Monotonous effectiveness of a blocking agent over time suggests that this agent impairs the maintenance, retrieval, or expression of memory, not its

consolidation. The aforementioned criterion is necessary and sufficient. Studies that report consolidation merely on the basis of time-dependent postacquisition changes in brain activity use a correlative approach that might supplement the aforementioned criterion, but by themselves do not prove that consolidation has taken place, as the observed changes might not necessarily be causally related to the stabilization or functional reorganization of memory.

SYNAPTIC CONSOLIDATION

Synaptic consolidation is universal; it has been described in all the species, preparations, and memory tasks investigated to date, so far as the task results in long-term memory. Long-term memory, in the context of discussion of synaptic consolidation, is conventionally defined as memory that lasts more than 24 hours, except in the study of long-term potentiation, a popular model of learning-related synaptic plasticity, in which even one hour is considered long. Listed below are selected common themes that emerge from the experimental data on synaptic consolidation (Dudai & Morris 2000):

a. Within a short time after training, new memories become resistant to interferences, or agents, which otherwise are capable of truncating the formation of long-term memory. These types of interferences or blockers include behavioral distractors, drugs, seizures, and anatomical lesions. The time window of susceptibility depends on the task and type of interference or blocker, and ranges from seconds to minutes (e.g., electroconvulsive shock in conditioning, Duncan 1949, McGaugh 1966), to hours (distractor tasks in motor skills, Shadmehr & Holocomb 1997; macromolecular synthesis inhibition in many types of tasks, see below).

b. The stabilization process is not a step-function, but rather various drugs or mutations can be used to dissect it into what appears to be intermediate phases in consolidation (e.g., DeZazzo & Tully 1995, Ghirardi et al. 1995, Grecksch & Matthies 1980, Rosenzweig et al. 1993, Winder et al. 1998). The time course of at least some of these phases is not a given, and could be altered by experimental manipulations, which may mimic in vivo stimuli and processes (Frey & Morris 1997). It is also unclear whether phases of consolidation must take place in a prescribed order for the consolidation to complete successfully.

c. The application of RNA or protein synthesis inhibitors during or immediately after training blocks the formation of long-term memory (Agranoff & Klinger 1964, Davis & Squire 1984, Freeman et al. 1995, Montarolo et al. 1986, Rosenblum et al. 1993). At least in the behaving animal, massive reduction in protein synthesis ($>90\%$) is required to achieve the effect. Usually, a similar transient reduction in macromolecular synthesis does not significantly affect perception, short-term memory, or either the retention or the retrieval of long-term memory once it has been established, with the single (important)

exception of application of these inhibitors immediately after retrieval, which is discussed below.

d. Intracellular signal transduction cascades[1], and particularly the cyclic adenosine monophosphate (cAMP) response element (CRE)-mediated modulation of gene expression by such cascades, are thought to play an important role in the consolidation of short- into long-term memory. This has been established in neuronal models of plasticity as well as in behaving animals (e.g., Deisseroth et al. 1996, Frank & Greenberg 1994, Kaang et al. 1993, Lamprecht et al. 1997, Yin et al. 1994). A prominent example is the cAMP cascade, which involves activation of a cAMP-dependent kinase[2], which phosphorylates and activates isoforms of cAMP-response element binding proteins (CREBs). The balance between activator and repressor forms of CREBs may be critical in triggering long-term cellular information storage (Bourtchuladze et al. 1994, Yin et al. 1994). CREB modulates the expression of CRE-regulated genes, including a number of immediate-early genes (IEGs), such as transcription factors that, in turn, regulate the expression of late response genes[3]. Other IEGs include cell adhesion molecules, and enzymes that control the degradation of intracellular or extracellular proteins.

e. Processes of neuronal protein synthesis that correlate with and are required for consolidation are now known to be multiphasic, involving the concerted recruitment of synaptic and cell-wide mechanisms (Huber et al. 2000, Martin et al. 1997, Steward et al. 1998). It appears that the activated synapse is somehow "tagged," possibly by posttranslational modification of synaptic protein(s), or by reorganization of such proteins (Dudai 1989, Frey & Morris 1997, Katz & Halstad 1950, Martin et al. 1997). This results in a new local synaptic configuration, which itself might attract new proteins from the cell. In addition, proteins synthesized in the synapse itself may strengthen the tagging of this synapse, and/or serve as retrograde messages, which travel to the cell body and inform the nucleus about the change (e.g., Casadio et al. 1999). There is also modulation of gene expression in the nucleus, and production of new messenger RNAs (mRNAs) and proteins, which are funneled into the tagged synapse. Overall, the process is hence assumed to

[1]Intracellular signal transduction cascades are molecular pathways that decode extracellular signals, such as neurotransmitters or hormones, and convert the information into cellular response. These cascades commonly involve the operation of "second messengers," small molecules that transmit information from one macromolecular complex to another within the cell. cAMP is such a "second messenger."

[2]A protein kinase is a ubiquitous type of enzyme that modifies proteins and regulates their function by catalyzing the addition of a phosphoryl group, a process called phosphorylation.

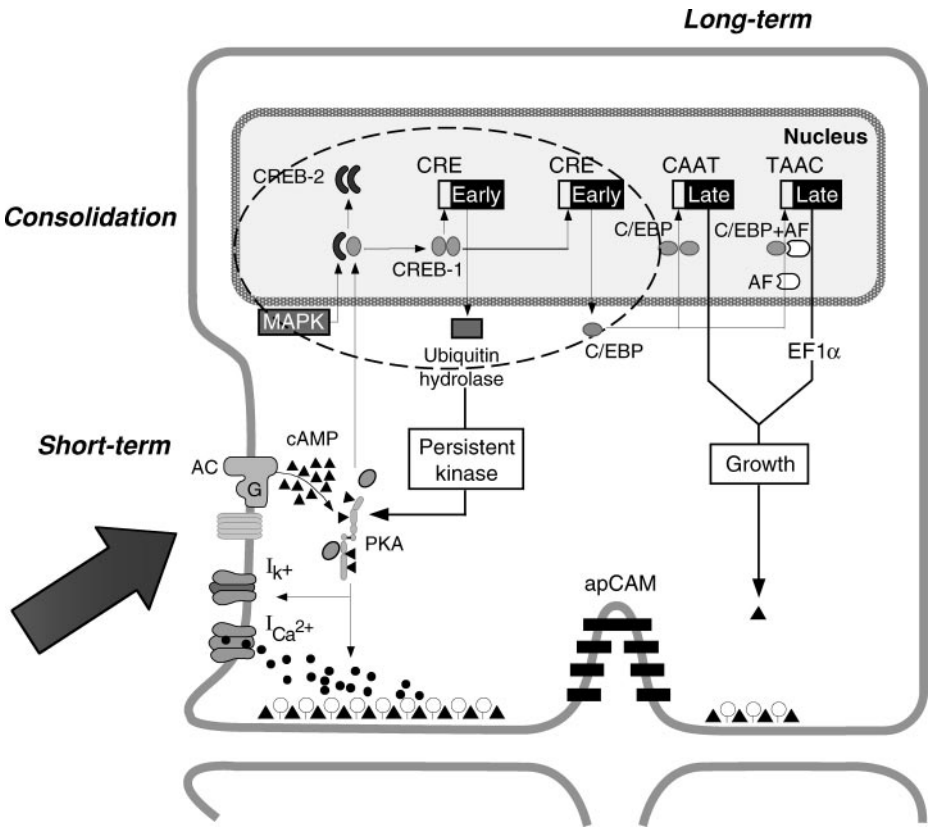
[3]Immediate early genes (IEGs) are genes whose products are induced rapidly and transiently in cells, such as nerve cells, in response to extracellular stimulation, via the operation of intracellular signal transduction cascades. Late response genes are genes whose products are induced in response to extracellular stimulation with a delay of a few hours.

involve coordination between the activated synapse and the nucleus, which possibly optimize exploitation of the metabolic resources of the neuron and the specificity of the long-term change (Dudai & Morris 2000).

f. The long-term changes in the synapse involve trafficking of new receptor molecules and possibly other proteins into the synaptic membrane, and alteration in the association of receptors with cellular cytoskeleton and signal transduction cascades (e.g., El-Husseini et al. 2002, Shi et al. 1999). In addition, there is evidence that long-term synaptic plasticity and long-term memory are correlated with morphological changes in synapses (e.g., Bailey & Kandel 1993, Weiler et al. 1995).

THE STANDARD MODEL OF SYNAPTIC CONSOLIDATION

The above and additional findings served as the basis for the formulation of the standard model of synaptic consolidation (Figure 2). This model posits that memory traces can exist in at least two forms: short-term and labile, and long-term and



stable (Hebb 1949; as noted above, it is now recognized that intermediate forms exist as well). The short-term trace may decay, or mature into a long-term form, or, alternatively, the short- and the long-term forms may develop in parallel. The physiological conditions that give rise to the long-term form are not yet fully identified but may involve suprathreshold neurotransmitter signal, or, probably more prevalent, coincidence of two or more inputs, including neuromodulatory ones.[4] These signals initiate or promote synaptic consolidation. This involves posttranslational modification of synaptic proteins, activation of transcription factors, modulation

[4]In which case diffused neuromodulatory systems, hormones, and the amygdalar complex play a decisive role; they probably play a role in system consolidation as well (McGaugh 2002).

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Figure 2 The standard model of synaptic consolidation. Information (left arrow) triggers intracellular signal transduction cascades, leading to modification of synaptic proteins and subsequently to alteration of synaptic excitability and of the amount of neurotransmitter(s) released onto target nerve cells. According to this dominant model, the same or interconnected intracellular signal transduction cascades can also activate transcription factors, leading to modulation of gene expression (first early genes, early, later late genes, late; see also the section on Synaptic Consolidation in the text). This culminates in long-term modification of synaptic proteins and in synaptic remodeling and growth. The activation, expression, and function of certain transcription factors and early genes is an essential part of the cascade of events, which occurs during a limited time window during and immediately after training, and can be disrupted by several types of agents, including inhibitors of protein synthesis. This time window is assumed to correspond to synaptic consolidation (a selection of the molecular species involved are schematically depicted by the elliptic broken line). The process, however, involves not only the synapse but also the cell body and nucleus. The scheme is highly simplified and depicts only a few presynaptic processes. AC, adenylate cyclase, an enzyme that generates the intracellular messenger cAMP; AF, activation factor, regulates transcription; apCAM, a cell adhesion molecule, takes part in synaptic remodeling; CAAT, a nucleotide sequence that regulates transcription; cAMP, cyclic adenosine monophosphate, a ubiquitous intracellular messenger; CRE, cAMP response element, regulates gene expression; C/EBP, enhancer binding protein, another protein that regulates gene expression; CREB, CRE binding protein; EF1α, elongation factor 1α, required for protein synthesis; I_{K+}, potassium channel, controls synaptic excitability; $I_{Ca2+,}$calcium channel, controls synaptic excitability, signal transduction cascades, and neurotransmitter release; kinase, an enzyme that modifies proteins by phosphorylating them; MAPK, mitogen activated protein kinase, a family of kinases that respond (indirectly) to extracellular stimuli; ubiquitin hydrolase, an enzyme that takes part in degradation of proteins. The figure is based on studies of simple learning in defensive responses in the mollusk *Aplysia* (e.g., Milner et al. 1998), but is considered to apply to other systems as well.

of gene expression at synapses and cell body, reorganization of synaptic proteins including membrane receptors and cytoskeletal elements, all together culminating in synaptic remodeling, which is assumed to make the trace stable. All this is fitted into a conceptual framework that depicts the cellular manifestation of memory consolidation as a growth or developmental process. In both development and use-dependent plasticity, gene expression is regulated by extracellular signals, and in both cases, similar ubiquitous intracellular signaling cascades, such as the cAMP and the mitogen-activated protein kinase (MAPK) cascades, are recruited, and cellular remodeling and growth occur. A caveat is, however, appropriate: It is not yet proven that in real life, synaptic remodeling and growth indeed encode the new memory and embodies its persistence over time. Alternatively, it could subserve homeostasis or expansion of computational space for new anticipated needs of the activated circuit (Dudai 2002a).

SYSTEM CONSOLIDATION

The evidence for system consolidation stems from both human and animal studies. Here is a selection of the major findings:

a. Many human "global" amnesics, as noted above, display temporally graded retrograde amnesia for declarative memory, i.e., remote memory is spared relative to more recent memory (Burnham 1903, Ribot 1882, Russell & Nathan 1946, Squire & Alvarez 1995). Other cases, however, display dense ungraded retrograde amnesia extending over many decades. Whereas the temporally graded retrograde amnesia is most often associated with damage to the medial temporal lobe, including the hippocampal formation and associated cortici, flat extensive retrograde amnesia usually also involves damage to neocortex in the lateral and anterior temporal lobe (Squire et al. 2001). Furthermore, amnesic patients with medial temporal lobe lesions can still recollect remote autobiographical events in great detail (Bayley et al. 2003). All this is commonly taken to imply that the medial temporal lobe, including the hippocampal formation and associated cortici, is required for intact long-term declarative memory, but its role is limited in time, and storage is ultimately relegated to the neocortex.

b. The memory of "global" amnesics for nondeclarative information is often spared, sometimes to a remarkable degree. This indicates that the mediotemporal lobe is not required for the consolidation (or other memory faculties) of skills and other forms of nondeclarative memory (e.g., Brooks & Baddeley 1976, Cohen 1984, Corkin 2002, Knowlton et al. 1996, Milner et al. 1968). Even when postmorbid facts are acquired, this seems to be done in a nondeclarative manner (Bayley & Squire 2002).

c. The immediate recall of dense amnesics, such as patient H.M. (Corkin 2002, Scoville & Milner 1957), is in the normal range. Taken together with the retention of old memories, this implies that the deficit in amnesia is not in acquisition, short-term memory, or overall storage capabilities, but rather in

either consolidation or retrieval. The temporally graded amnesia is taken as evidence that the deficit is in consolidation (but see below).

d. Selective lesions to the hippocampal formation or entorhinal cortex in laboratory animals, including mice, rats, rabbits, and monkeys, produce postlesion temporally graded amnesia, extending weeks, in several types of memory tasks (Cho et al. 1993, Clark et al. 2002, Kim & Fanselow 1992, Kim et al. 1995, Kubie et al. 1999, Winocur 1990, Zola-Morgan & Squire 1990). This is congruent with the aforementioned human amnesia data and with the notion that the hippocampal formation and related structures have a temporally limited role in long-term memory.

e. Some studies of functional brain imaging unveil postacquisition temporally graded activity in mediotemporal structures in the human brain (Haist et al. 2001), and in the hippocampal formation in mice (Bontempi et al. 1999), which suggests that time-dependent reorganization of brain circuitry is involved in the formation of long-term memory.

THE STANDARD MODEL OF SYSTEM CONSOLIDATION

The above findings served as the basis for the formulation of the standard model of system consolidation (Figure 3). This model posits that long-term memories that depend in their encoding on the hippocampal formation and related structures in the mediotemporal lobe and the telencephalon are initially registered, probably in different formats, in both the hippocampal formation and the relevant neocortex. The stabilization of these internal representations is assumed to involve synaptic consolidation, which is achieved within minutes to hours. In parallel, or as a consequence, a process of system consolidation is initiated, characterized by much slower temporal kinetics. In this process the trace reorganizes over a period of weeks or more, shifting the burden of retention to the neocortex, so that ultimately the neocortex can independently maintain the specific internal representation and actualize it in retrieval. It is not yet known what triggers system consolidation, but the most parsimonious account is that over time, upon recurrent activation of the hippocampal trace either in explicit recall or in implicit processing (e.g., sleep), the hippocampal formation and related structures send synaptic messages to neocortical neurons, and these messages trigger synaptic consolidation locally.

DOES SYSTEM CONSOLIDATION OCCUR ONLY IN DECLARATIVE SYSTEMS?

The textbook account of system consolidation is that it applies to hippocampal-dependent memory only, whereas in nondeclarative systems, which do not depend on the hippocampal formation and related structures, consolidation is restricted to the same circuits that have encoded the information on-line. That nondeclarative memories do not undergo system consolidation should not, however, be taken as

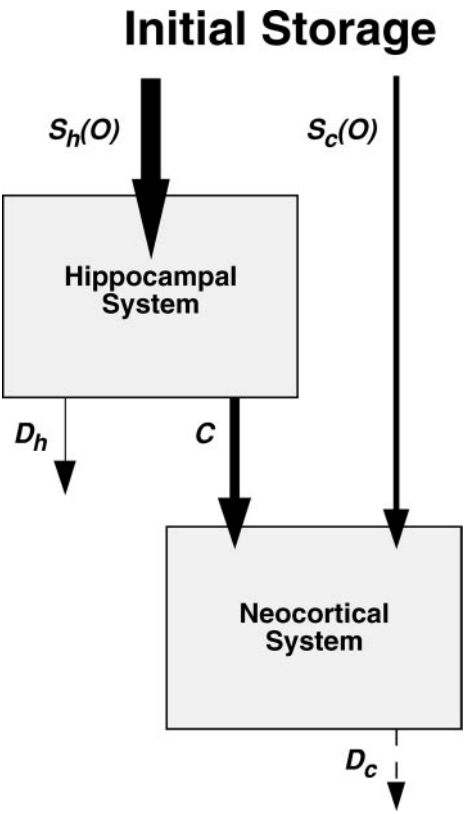

Figure 3 The standard model of system consolidation is depicted in a flowchart. Initial storage, i.e., encoding and registration of the perceived information (Dudai 2002a), occurs in both the hippocampal system and the neocortical system. $S_h(0)$ and $S_c(0)$ represent the strength of the initial hippocampal and neocortical traces, respectively. These traces are expected to differ, with the hippocampal one probably representing a compressed version of the internal representation. The hippocampal representation later becomes active either in explicit recall, or in implicit processes such as sleep. This gives rise to reinstatement of the corresponding neocortical memory, resulting in incremental adjustment of neocortical connections, probably involving local, synaptic consolidation. In parallel, memory also decays, faster in the hippocampus (D_h) than in the cortex (D_c). The net result is that memories initially dependent on the hippocampus gradually become independent of it. In reality this happens over weeks or longer. The hippocampal system can hence be viewed not only as a memory store but also as a teacher of the neocortical system. This process (C, rate of consolidation) is proposed to allow the hippocampal system to rapidly learn new information without disrupting old memory stored in the neocortex, while at the same time allowing gradual integration of the new information into the older, structured information. Adapted from McClelland et al. (1995).

an established given. There are actually two questions here: (*a*) Is there a process of slow circuit reorganization in nondeclarative systems that continues after the initial wave of synaptic consolidation has been accomplished, and in which parts of the circuit become dispensable for retention or retrieval, and (*b*) Is there spread of the trace to new circuits that did not subserve encoding? Motor skill learning provides a suitable system to investigate these questions. Multiple brain areas subserve this type of task, including among others the primary motor cortex, other neocortical areas, the cerebellar cortex and deep nuclei, and the striatum (Doyon et al. 1997, Karni et al. 1998, Kleim et al. 2002, Nudo et al. 1996, Ungerleider et al. 2002). It has been reported that within six hours after completion of practice in a visuomotor pursuit task, the brain engages new regions to perform the task, as visualized by positron emission tomography imaging; specifically, this involved a shift from prefrontal cortex to posterioparietal cortex and cerebellar structures (Shadmehr & Holocomb 1997). Brain reorganization of task-related activity has also been demonstrated by fMRI in the brain of subjects acquiring skilled sequential finger movement (Karni et al. 1998, Ungerleider et al. 2002). Here changes in the primary motor cortex (M1) were detected very early in learning, in parallel with rapid changes of activity in the cerebellum, striatum, and other motor-related cortici, which was followed by slowly evolving reorganization of M1 over weeks (Ungerleider et al. 2002). A model has been suggested on the basis of these studies, which proposes that early in learning there is transfer of experience-dependent changes from the cerebellar cortex to the dentate nuclei of the cerebellum, and then later from a cerebellar-cortical to a striatal-cortical network (Doyon et al. 2002). The protocol used, however, involved incremental learning; therefore the observed changes could not be attributed to consolidation per se, but rather might be due to extended practice. In another study, repetitive transcranial magnetic stimulation of M1, but not other brain areas, was reported to disrupt the retention of the behavioral improvement on skilled finger-movement tasks if it was applied within about six hours of training (Muellbacher et al. 2002). Basal motor behavior, task performance, motor learning by subsequent practice, or recall of the newly acquired motor skill were not affected. This was taken to indicate that M1 is involved in the consolidation of motor skill within a few hours of practice.

It is also noteworthy that the evidence for the requirement for sleep, particularly dream sleep, in memory consolidation (and see System Consolidation section above) is particularly prominent in nondeclarative tasks, which suggests that consolidation lasts for several hours (Jenkins & Dallenbach 1924, Maquet et al. 2003, Pennartz et al. 2002, Stickgold et al. 2001).[5] Yet a few hours, whether asleep (ibid.)

[5]Again this is a place to pay tribute to Quintillian (first century A.D.) and Hartley (1810), harbingers of the study of the relationship between sleep and memory. Of particular interest is the view of Hartley: "The wildness of dreams seems to be of singular use to us, by interrupting and breaking the course of our associations. For, if we were always awake, some accidental associations would be so much cemented by continuance, as that nothing could afterwards disjoin them; which would be madness." This is echoed in a more recent hypothesis on the relevance of dream sleep to consolidation (Crick & Mitchison 1983).

or awake (Brashers-Krug et al. 1996), is still within the accepted time window of synaptic consolidation. At the time of writing, no evidence is available for more prolonged consolidation of skill. Nor is there evidence that the slow reorganization of the brain areas, which is suggested by the evolving patterns of brain activity over days and weeks in certain skill acquisition protocols, is a signature of the representation of a specific item in memory, let alone indication that this representation invades new circuits, that part of the original circuits become dispensable for recall, or that it is at all consolidation and not transition among acquisition strategies. The resolution of these issues could benefit from selective lesion experiments in laboratory animals, similar to the approach used in investigation of the consolidation of declarative memory in the mediotemporal lobe.

WHY CONSOLIDATE?

Why do memories consolidate in the first place? One could envisage a situation in which newly encoded memories stabilize instantaneously (this is what some opponents of the consolidation theory propose; see Reservations Concerning the Consolidation Theory section below), or that memories never really stabilize at all (and this is what some orthodox proponents of reconsolidation hypothesis might claim; see Reconsolidation section below). This question could be applied to both synaptic and system consolidation, and in each case, it could be discussed at different levels of analysis. Two levels of analyses, following the type-of-level analysis by Marr (1982), are the most pertinent to the current discussion: the level of the computational theory, i.e., what is the goal of the system and what is the logic of the strategy by which the computations are carried out; and the level of hardware implementation, i.e., how are the algorithms that execute the computations implemented in the biological hardware? One generic possibility at the level of computational theory, which applies to both synaptic and system consolidation, is that instant stabilization of every encoded internal representation is bound to waste brain computational space on useless items and hence rapidly reduce processing and storage capacity. Another possible explanation is that in the poststimulus time window of consolidation the newly acquired information is particularly malleable and readily associates with other inputs, of either on-line or off-line sources, so that information is bound together in a more useful manner and meaningful narratives are more easily formed. Again, this type of potential explanation has been suggested for both synaptic and system consolidation. In the former, it has been linked to the finding that activated synapses are tagged for a short postactivation period and during this tagging period could be stabilized in response to concurrent activity in other synapses on the same neuron (Frey & Morris 1997), permitting generalization and binding at the synaptic level within the circuit (Dudai & Morris 2000; for a harbinger of this notion see Landauer 1969, itself a sequel to the idea that consolidation is a period of reinforcement; Thorndike 1933; see also White 1989). But the more popular version of this type of explanation was applied to system consolidation in the corticohippocampal system, and is supported by modeling (McClelland & Goddard 1996, McClelland et al. 1995; Figure 3). Briefly, the suggestion is that new episodes are stored in the

hippocampal formation, which recurrently replays them over time to the neocortical system, interleaving them with other encoded experiences. This process allows the cortex, according to the model, to gradually discover the structure in ensembles of experiences, leading to categorization and generalization of cortical memories, which is clearly advantageous for cognitive function. Furthermore, according to this model, having these complementary learning systems in the hippocampus and neocortex allows the brain to rapidly learn new on-line events without disrupting the structure of off-line information, and then to integrate these new events properly with previously stored experiences. This type of processing might be particularly suitable for declarative memories, considering that a proposed primitive of such memories is their flexibility, transitivity, and generalizability (Cohen et al. 1997, Eichenbaum 1997). Actually, in this respect, it is the hen-and-egg type of issue: Did the system evolve this way to promote the aforementioned primitives of declarative memory, or did these primitives of declarative memory emerge as by-products of system evolution, which had a different, yet unknown selective pressure?

Which brings us to an utterly different type of putative explanation for consolidation. The explanations proposed so far assume that the system works in a particular way because this is adaptive, more generally, because natural selection is an optimizing agent. These explanations are dubbed adaptionist or Panglossian[6] (Gould & Lewontin 1979). But it is also possible that the system is the way it is because of accumulative, built-in operational constraints, irrespective of the assumed adaptivity, or alternatively that the system is still far from optimization. Hence the possibility should also be entertained that consolidation is a spin-off of the constraints imposed on biological memory by the design and maintenance of biological systems, rather than by functional properties selected in evolution. This possibility might apply particularly to synaptic consolidation, where the standard dogma depicts processes that are engaged to overcome the brief life span of proteins due to their molecular turnover, itself a mechanistic constraint of biological material, which might be advantageous in development or housekeeping but not necessarily in memory systems.

RESERVATIONS CONCERNING THE CONSOLIDATION THEORY[7]

Almost from its outset the consolidation theory was not without its share of criticism and skepticism. These are commonly brought up in the context of discussions of system consolidation but are relevant to synaptic consolidation as well. They

[6]Dr. Pangloss, the mentor of Voltaire's Candide, was an incurable optimist, justifying every disaster under the sun by the a priori assumption that everything is always for a good cause.
[7]The term "consolidation theory" is in common use in the literature. It is not really a theory in terms of abstract laws and their interrelationships, but rather a hypothesis or a generalization, as currently is any other "theory" in biology. The term is used here to refer to both synaptic and system consolidation, although each of these processes could be considered independently.

stem from findings obtained in the study of experimentally induced amnesia in laboratory animals and of cases of human amnesia. There are two levels of criticism. One questions the mere concept of consolidation. The other doubts whether the standard models are valid.

a. *Spontaneous recovery*. Over the years there were multiple reports in the animal literature that memory could recover spontaneously after amnestic treatment (e.g., Lewis et al. 1968, Miller et al. 1974). This was taken to imply that consolidation blockers do not prevent the formation of a long-term trace but rather block its expression.

b. *Reminder effects*. Similarly, a substantial number of studies have reported that in laboratory animals the retrograde amnesia produced by agents regarded as consolidation blockers could be reversed by reexposure to the conditioned stimulus (CS) alone (reattempted retrieval, reminder), to the unconditioned stimulus (US) alone (reinstatement), to stimulating drugs, or even to the amnestic agent[8] (Bradley & Galal 1988, DeVietti & Hopfer 1974, Gordon & Mowrer 1980, Hinderliter et al. 1975, Mactutus et al. 1982, Miller & Springer 1972, Quartermain et al. 1970). This implies that the consolidation blockers used under the conditions described do not block the formation of a long-term trace, but rather cause a deficit which can later be remedied, so that the latent trace resurfaces; or, in other words, that the deficit caused is not in long-term storage but rather in retrieval. Several related possibilities have been proposed considering the nature of the retrieval deficits, including that the amnestic treatment induces a specific internal state, resulting in state-dependent learning, so that the original memory cannot be retrieved unless the original state is reinstated; or that the amnestic agent provides cues that must be reprovided to allow retrieval to proceed (for a recent recount of this type of interpretation, see Miller & Matzel 2000, Millin et al. 2001).

c. *Memory in amnesic patients*. More than 30 years ago, Warrington & Weiskrantz (1970) reported that amnesic patients could remember verbal material if tested in a protocol that provides partial information about the target. Hence the performance of these patients was similar to nonamnesic controls when fragmented target words were presented for identification in the test (1–11 minutes posttraining), but not when the patients were requested to recall these words or recognize them in a mixed list of new and old words. The authors therefore suggested that it is inappropriate to characterize the amnesic syndrome as being a failure of registration or consolidation of information, but rather, it is a retrieval deficit: Given the appropriate retrieval cues, the memory becomes available. This proposal, which later came to evoke recurrent debates in the amnesia literature, is in line with the aforementioned

[8]Although the various manipulations differ with regard to the part of the internal representation they are expected to trigger, it is convenient to term them all as "reminders," and their effects as "reminder effects."

reminder effects observed in animal studies. Another type of opposition to the "standard" model of system consolidation refers specifically to the notion that in this process, episodic memory becomes gradually independent of the hippocampal formation. Here the main arguments are that (*a*) In many amnesic patients the retrograde amnesia is not temporally graded; (*b*) When temporally graded retrograde amnesia is detected, it is task dependent; (*c*) In some cases the so-called temporally graded retrograde amnesia covers decades, so that for all practical purposes the hippocampal formation appears to be involved in the memory throughout life (Moscovitch & Nadel 1998, Nadel & Moscovitch 1997); and (*d*) Some functional neuroimaging studies show equivalent activation of the hippocampal formation in healthy volunteers in recollection of events up to 20 years ago (Ryan et al. 2001; but see Haist et al. 2001 for different conclusions concerning the activation of medial temporal lobe structure in remote memory, particularly the entorhinal cortex). This observation is congruent with the idea that damage to the hippocampal formation causes retrieval deficits. Taking these types of findings into account, Nadel & Moscovitch (1997) have proposed an alternative to the standard model of system consolidation, in which the hippocampal formation is involved in some types of memory (episodic, spatial) for as long as these memories endure. In their model, the entire hippocampal-neocortical system encodes the trace in a distributed manner, but over time, repetitive reactivation of the trace results in hippocampal-dependent formation of multiple, related traces that facilitate the retrieval of an episode using a variety of cues, so that more extensive lesions are required to delete more remote memories. Note, however, that some version of system consolidation is still postulated in this model, because memory reorganization is assumed; only the idea that the role of the hippocampus is time-limited is rejected.

SELECTED RESPONSES TO THE RESERVATIONS

It could be claimed that spontaneous recovery occurs because the blockade of the consolidation process was incomplete and the process, or parts of it, ultimately escape inhibition. Further, many studies fail to find spontaneous recovery of amnesia, and although a negative result, it is a consistent one. The observation that the hippocampal formation lights up in functional neuroimaging of episodic retrieval, including of very remote memories, is itself not proof that this region is obligatory for retrieval. And as to retrieval accounts of amnesia in general, the question could be raised: What is it that is consolidated when a memory becomes long-term, and shouldn't the internal representations of states, cues, or hypothetical indices for retrieval be considered an integral part of the engram, and hence shouldn't their encoding consolidate as well? If one accepts this broader view of consolidation, namely that consolidation is not only stabilization of the persistent trace but also its maturation into a form suitable for future retrieval, then the retrieval type of explanation does not really contradict the consolidation theory. And as to the residual

memory capabilities of human amnesics: The priming data used to support the retrieval deficit hypothesis are accounted for by the fact that "global" amnesics are damaged only in declarative, not in nondeclarative, memory systems such as the one that supports repetition priming (Schacter 1987, Squire 1987). Last, in general, in evaluating the status of the consolidation theory, one should also consider the rich literature that describes in remarkable detail molecular and cellular processes and mechanisms that correlate with synaptic consolidation, and whose blockade blocks long-term memory. Indeed, much more evidence is still needed to establish whether these processes and mechanisms embody the new long-term internal representation, or are only auxiliary to its formation (Dudai 2002a, Martin et al. 2000); yet the molecular and cellular data, combined with the pharmacological data and corroborated by some morphological evidence, strongly reinforce the now-classical notion that the trace is indeed transformed from a short-term, more labile form, into a long-term, more stable form, either in serial or parallel processes, and that this transformation is not instantaneous but requires postexperience time (Hebb 1949). Having said all this, even orthodox believers in the consolidation theory should still keep at the back of their minds the fact that a body of literature questions their faith. Pieces of puzzling data still call for explanation. Therefore, to assume that the current textbook models of consolidation are faithful to reality is a bit naive.

DO MEMORIES RECONSOLIDATE?

The standard model(s) of consolidation are conventionally taken to imply that for any memorized item, consolidation starts and ends just once. But currently, a hotly debated issue in memory research in general and in consolidation research in particular is whether this assumption is valid. Note that even if it is not, this does not annul the mere concept of a consolidation phase—it just modifies it to mean that the stability is under certain conditions ephemeral. The debate is not at all new, but has been resurrected in recent years. In 1968, Misanin et al. reported that electroconvulsive shock (ECS), a known amnestic agent, leads to memory loss if administered immediately after retrieval, 24 hours posttraining, of a seemingly consolidated, long-term conditioned passive-avoidance memory. Similarly, Schneider & Sherman (1968) reported that in a passive-avoidance task, rats became amnesic if ECS was administered immediately after noncontingent presentation of the US (i.e., a reinstatement trial) even if this was done six hours after CS–US conditioning, at which time the memory was known to become resistant to ECS. These reports were followed by additional reports of such apparent reconsolidation in other tasks or using other amnestic agents (e.g., Judge & Quartermain 1982, Lewis & Bergman 1973, Lewis et al. 1972). Controls were presented to show that this was specific to the activated memory, and not reinstatement of a general internal state. The basic idea that emerged from these experiments was that it is not the time since encoding that determines the susceptibility of a trace to interventions, but rather the functional state of the trace: An active (retrieved) trace can be truncated, but also augmented (Sara 2000); an inactive (stored) trace is immune

to such manipulations (Lewis 1979). Others could not, however, replicate the reconsolidation phenomenon (Dawson & McGaugh 1969). Still others reported that the blocking of recall was transient only (Mactutus et al. 1979). Besides supplying the opposition of the consolidation theory with additional ammunition to criticize the idea that in consolidation memories are permanently stabilized, the reconsolidation reports should have provoked much attention and should have been followed by intense attempts to clarify the picture once and for all because of the obvious theoretical and clinical implications. This did not happen. There were multiple reasons for this decay of active interest, in addition to the aforementioned inconsistencies in the findings among different laboratories. First, the reconsolidation idea was not easy to reconcile with the zeitgeist. And second, the neurobiology of memory went cellular and molecular, and systemic interventions were not thought to be as fashionable as before; a similar trend was noted at about the same time in the study of synaptic consolidation in experimental animals (Dudai 2002a).

A new phase in the life of the reconsolidation hypothesis started a few years ago. Following additional papers on the topic (e.g., Bucherelli & Tassoni 1992, Przybyslawski & Sara 1997, Przybyslawski et al. 1999, Roullet & Sara 1998, Sekiguchi et al. 1997), Sara (2000) reviewed the field in detail, arguing more or less that reconsolidation is not a myth and should not be neglected. At about the same time, Nader et al. (2000) reported the phenomenon in fear conditioning, targeting directly a brain circuit assumed to subserve this memory. They trained rats on elemental, Pavlovian fear conditioning to associate a tone with foot shock. A common measure of the conditioned response in this paradigm is the immediate freezing to the tone. The consolidation of this type of memory can be blocked by microinfusion of the protein synthesis inhibitor anisomycin into the lateral and basal nuclei of the amygdala (LBA) immediately after training. Nader et al. reported that the consolidated fear memory can return to a labile state, in which local microinfusion of anisomycin into the LBA immediately after the retrieval of the fear memory, but not six hours afterward, produces amnesia on subsequent tests. This happened regardless of whether retrieval was 1 or 14 days after conditioning. The same treatment with anisomycin in the absence of memory reactivation left memory intact. Their conclusion was that consolidated fear memory, when reactivated, returns to a labile state that requires de novo protein synthesis for new consolidation, i.e., reconsolidation. In their paper Nader et al. (2000) did not provide evidence that the amnestic effect is long-term, rather than a transient drug effect. Later, however, the same group determined that the deficit lasts for at least three weeks (K. Nader, personal communication).

The Nader et al. (2000) report became highly visible and additional studies soon followed. Taubenfeld et al. (2001) reported that anisomycin impairs memory on an inhibitory avoidance task if injected systemically immediately after retrieval of a consolidated memory. Interestingly, whereas consolidation of this task depends on hippocampal protein synthesis, direct infusion of anisomycin into the hippocampus after retrieval had no effect on memory. Microinfusion of oligodeoxynucleotides antisense to the transcription factor β(C/EBPβ) into the hippocampus impaired memory only after acquisition but not after retrieval, which led the authors to

propose that the consolidation of new but not reactivated memory requires this transcription factor, and also that brain areas other than the hippocampus (amygdala?) are involved in postretrieval consolidation. Kida et al. (2002) used transgenic mice with an inducible and reversible suppressor of the transcription factor CREB (see Synaptic Consolidation, above), and found that CREB is crucial for the consolidation of long-term contextual fear conditioning as well as for the stability of retrieved consolidated memory, but not for the encoding, retention, or retrieval of such memory. Using local microinfusions of anisomycin, Debiec et al. (2002) reported that de novo protein synthesis in the hippocampus is required for both the consolidation and the reconsolidation of contextual fear conditioning. Again, reactivation of the trace was essential for the effect to take place, and the amnesic deficit persisted after several weeks. Reconsolidation has since been observed in object recognition in rats, where mitogen-activated protein kinase (MAPK; see Figure 2) was identified as critical for the process, similar to its role in consolidation of a new memory (Kelly et al. 2003). Data construed as reconsolidation, dependent on protein synthesis and NMDA-type of glutamatergic receptors, were also reported in the crab *Chasmagnathus* in contextual fear conditioning (Pedreira et al. 2002). It is highly likely that between the time of writing of this review and its publication, numerous laboratories will report additional reconsolidation studies in various systems.

Whereas Nader et al. (2000) and Debiec et al. (2002) reported that reactivation-induced reconsolidation of fear conditioning can be obtained weeks after training, Milekic & Alberini (2002), using the inhibitory avoidance task, reported a temporal gradient of sensitivity to protein synthesis inhibition (achieved in this case by systemic rather than local administration of anisomycin). Susceptibility to disruption of the reactivated memory was very high at 2 days posttraining, was significant but lower at 7 days, but disappeared at 14 days. This implies that in this task and protocol, memories do become stabilized and immune to the effects of consolidation blocker after a period that is longer than that of synaptic consolidation, but much shorter than the life span of the memory.

Still other studies of the postretrieval effect of a consolidation blocker did not unveil lability of the original trace. Rats conditioned to associate a taste with delayed toxicosis (conditioned taste aversion, CTA) reject the conditioned taste for months afterwards. Microinfusion of anisomycin into the insular cortex, which contains the taste cortex, immediately before or after conditioning, prevents the consolidation of CTA. Once formed, CTA memory can be extinguished by presenting the taste in the absence of malaise. If immediately before or after the retrieval of taste aversion in an extinction protocol, anisomycin is microinfused into the insular cortex, extinction is blocked, whereas the original trace is spared (Berman & Dudai 2001, Berman et al. 2003). Similarly, microinfusion of anisomycin into the basolateral nucleus of the amygdala immediately after retrieval resulted in inhibition of CTA extinction rather than in diminution of the original association (Bahar et al. 2003). Vianna et al. (2001) reported that retrieval of memory of fear-associated inhibitory avoidance initiates extinction, which is blocked by protein synthesis inhibition in the hippocampus, again sparing the original trace. These studies are

compatible with the idea that extinction is relearning rather than unlearning, and that the resulting memory, like any other long-term memory, undergoes protein synthesis–dependent synaptic consolidation. The original trace, however, does not seem to become labile in retrieval in these protocols.

There might be an explanation for these differences. In the study of Nader et al. (2000) on fear conditioning, the training and retrieval protocols do not lead to significant extinction upon retrieval, and the original trace is reported to enter a protein synthesis-dependent labile state; in the studies of Berman & Dudai (2001) and Vianna et al. (2001), the training and retrieval protocol results in significant extinction, and the original trace does not seem to enter a protein synthesis–dependent labile state. One possibility is, therefore, that the differences in the postretrieval lability of the trace are related to the retrieval protocol used (Dudai 2002b) and specifically to the interbalance or competition between the original trace (of the CS–US association, conventionally termed the excitatory trace) and the new trace (the CS–no US, conventionally termed the inhibitory trace) (Nader 2003). Eisenberg et al. (2003) recently found evidence that among competitive associations, the association that retains or gains behavioral control after the retrieval session, is the one that becomes sensitive anew to disruption by certain treatments that also block consolidation. Hence, if in CTA in the rat, the training is made intensive and the memory more robust and resistant to extinction, microinfusion of anisomycin into the insular cortex immediately after retrieval impairs performance guided by the original trace. In contrast, if the training allows extinction, the same treatment blocks the newly developing CS–no US association, as previously described by Berman & Dudai (2001). Similarly, if in shock avoidance in the *Medaka* fish, an anesthetic is administered in retrieval early in extinction training, when extinction has not yet developed, the original association is inhibited; if, however, the same treatment is applied in a later retrieval session, the new trace—of the CS–no US association—is impaired. The impairment, however, does not reflect erasure of the trace: In both cases reinstatement could later be detected by readministration of the unpaired US (M. Eisenberg, T. Kobilo, & Y. Dudai, in preparation). It thus seems that the stability of a memory item upon its retrieval is inversely correlated with the trace dominance (i.e., its control of behavior at that point in time), but loss of stability does not result in irreversible corruption of the entire trace. This observation notwithstanding, the stability$\sim$f(1/dominance) rule might account for some of the discrepancies in the reconsolidation data so far.

DIFFERENCES BETWEEN SYNAPTIC CONSOLIDATION AND POSTULATED RECONSOLIDATION

Scrutiny of the reconsolidation or attempted-reconsolidation data indicates that postretrieval consolidation does not recapitulate faithfully the consolidation of a new trace. First, the sensitivity of the two processes to consolidation blockers seems to be different. Both increased and decreased sensitivity have been reported. Deeper cooling was required to block consolidation compared to reconsolidation in shock

avoidance in the rat, which suggests that reconsolidation is more vulnerable to disruption (Mactutus et al. 1982). However, a dose of anisomycin similar to the dose used to block the original consolidation had no effect on presumed reconsolidation in a shock-avoidance task (Taubenfeld 2001), but doubling that dose had an effect in fear conditioning (Debiec et al. 2002), which suggests that reconsolidation is less vulnerable to disruption. Admittedly, these dose differences also raise the possibility that the anisomycin acts on different targets in each case. At the time of writing, no dose-response measurement of protein synthesis inhibition at the target was reported in any of the new attempted-reconsolidation studies except in the aforementioned CTA studies, and the mechanism of anisomycin action is hence inferred from other systems. Like many other drugs, this drug has multiple cellular targets (Kyriakis et al. 1994). Another difference is in the time course. The onset of amnesia was more rapid in cooling-sensitive reconsolidation of the shock-avoidance task (Mactutus et al. 1982), and the time window of anisomycin sensitivity was shorter in reconsolidation (Judge & Quartermain 1982; see also the brief time window of postretrieval consolidation in Berman & Dudai 2001). Furthermore, in CTA, the molecular processes of the original and the postretrieval consolidation processes, though sharing components, are not identical (Berman & Dudai 2001). This is also in line with the report of Taubenfeld et al. (2001), mentioned above, that the consolidation of new but not reactivated memory requires the transcription factor C/EBPβ.

A critical question concerning the reconsolidation studies is whether the detected amnesia is stable, or, alternatively, only a reflection of a transient latency of the trace, induced by the postretrieval treatment. The postretrieval-induced amnesia was shown to be stable in fear conditioning (Nader et al., personal communication). However, in earlier studies of reconsolidation in the rat (e.g., Mactutus et al. 1979), using cooling as the consolidation blocker, or in recent studies in the chick, using inhibition of macromolecular synthesis (Anokhin et al. 2002), the recall deficit obtained after retrieval was temporary. In CTA in the rat and in fear conditioning in *Medaka*, the blocked conditioned behavior did not recover spontaneously, but, as mentioned above, could be reinstated by the unpaired US (M. Eisenberg, T. Kobilo, & Y. Dudai, in preparation). Transiency of amnesia was also reported in part of the earlier reconsolidation literature, but it is noteworthy that the same groups also reported reversibility of the amnesia obtained following inhibition of the original consolidation (e.g., Mactutus et al. 1982; see also Radyushkin & Anokhin 1999).

THE POSSIBILITY OF SYSTEM RECONSOLIDATION

The evidence cited above (see also Nader 2003, Sara 2000) could be construed as indicating that upon reactivation in retrieval, traces undergo a consolidation process, which might be different in its temporal and molecular characteristics from the original consolidation, but still depends on de novo protein synthesis. The time window of this process (minutes to hours) and the dependence on protein synthesis implicate synaptic types of processes. Is there also evidence for system reconsolidation?

Because contextual fear conditioning is hippocampus dependent, it is a suitable system to put this question to a test. Debiec et al. (2002) did just that. In this system, like in other hippocampal-dependent memory tasks, the trace becomes practically independent of hippocampal function after a few weeks, i.e., it undergoes system consolidation. Debiec et al. showed that postactivation intrahippocampal microinfusion of anisomycin caused subsequent amnesia for the contextual fear memory, even when the reactivation was delayed for 45 days after training, when the memory is already hippocampal independent. This was taken to imply that reactivation of a hippocampus-independent memory caused the trace to again become hippocampus dependent. Further, Debiec et al. prepared rats with either sham or electrolytic lesions of the hippocampus 45 days after conditioning. Two other groups were treated identically except that immediately prior to surgery they received a reactivation (i.e., CS-induced retrieval) session. The hippocampal lesions (but not neocortical lesions) caused amnesia only in the animals that had received a reactivation session, and this amnesia did not show spontaneous recovery over a month. However, in contrast to system consolidation, which requires weeks to complete, the proposed system reconsolidation lasted for only two days.

The data of Milekic & Alberini (2002), mentioned above, showing a temporal gradient of sensitivity to protein synthesis inhibition in the hippocampal-dependent inhibitory avoidance task, are incongruent with the notion that memories can reconsolidate long after system consolidation has been completed. A caveat, however, is appropriate here. The Milekic & Alberini study involves another type of memory and another intervention protocol (systemic administration of the blocker versus target-directed). Furthermore, because the sensitivity of consolidation and reconsolidation to inhibition of protein synthesis may vary (see above), it is possible that the temporally graded requirement for protein synthesis following memory reactivation might be altered by increasing the dose of the inhibitor, or by targeting it to brain circuits outside the hippocampus, such as the amygdala.

All in all, at the time of writing, there is indication for system reconsolidation in one system and protocol; the phenomenon, and its generality, await further analysis.

ON THE MULTIPLE VERSIONS OF THE RECONSOLIDATION HYPOTHESIS

The reconsolidation hypothesis assumes consolidation upon activation of the trace in retrieval (Lewis 1979; Figure 4).[9] Ample evidence from behavioral and neurobiological analysis indicates that retrieval could involve reconstruction of the

[9]For the sake of brevity and argument, the possibility of latent recurrent activation in maintenance or reorganization of the trace (e.g., McClelland et al. 1995; see also the section on System Reconsolidation) is not discussed. However, should such activation happen and reconsolidation apply, an interesting question arises concerning the ongoing potential frailty of at least some types of long-term memory traces.

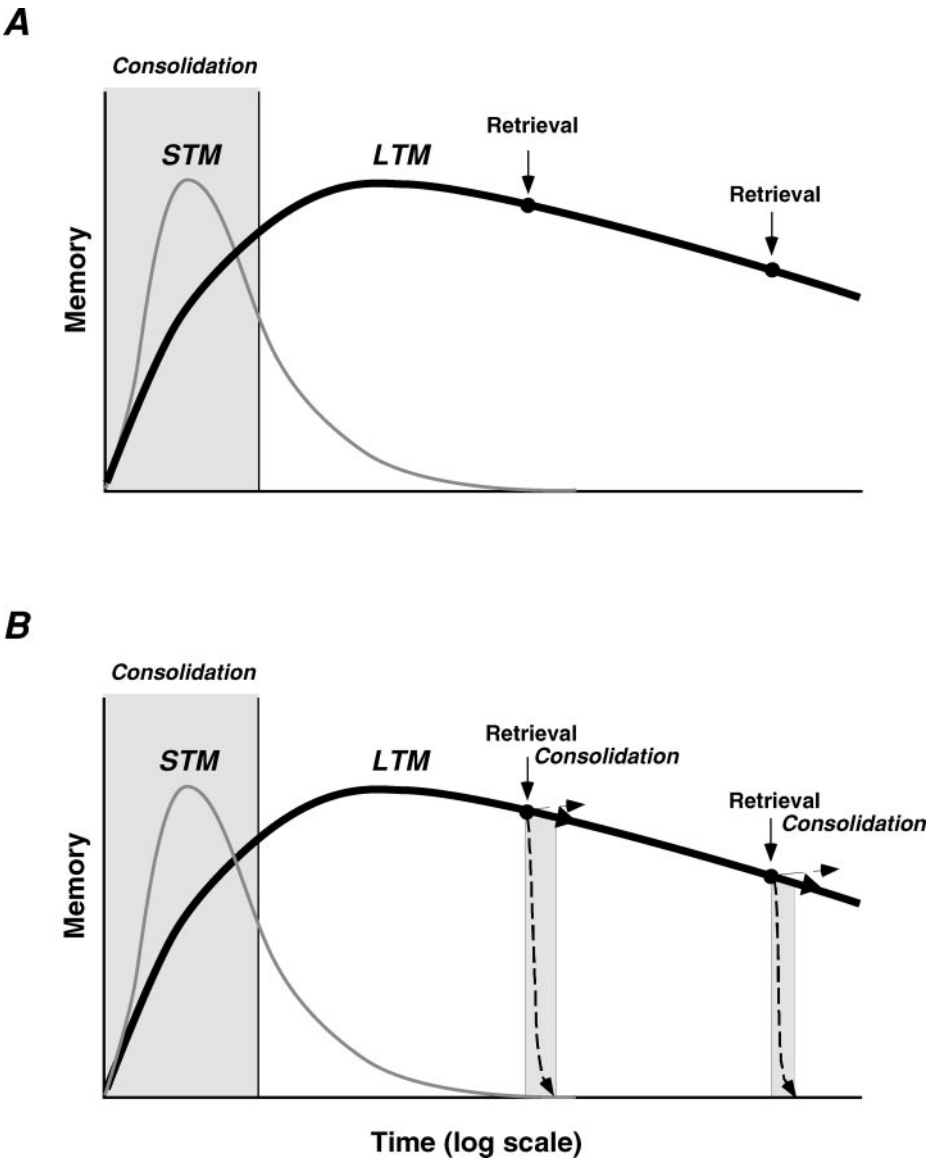

Figure 4 Two views of consolidation. (*A*) The standard models of consolidation are conventionally taken to imply that for any memorized item, consolidation starts and ends just once. (*B*) The revised model claims that consolidation can occur multiple times in the life of a memory item, specifically, after its activation in retrieval. The soft, trivial version of this hypothesis refers to the consolidation of new elements that are integrated into the old memory after its retrieval. The stronger versions refer to the possibility that the old memory reconsolidates after its activation and may become modified in the process.

trace, including its amalgamation with new information obtained in the retrieval situations (Bartlett 1932, Dudai 2002a, Schacter et al. 1998, Tulving 1983). This explains why in fact there are three versions to the reconsolidation hypothesis: a weak one, and two stronger ones. The "soft" or "weak" version states that upon retrieval the trace is updated but only the new parts of the modified trace undergo consolidation. This version is trivial, because it refers to consolidation of a new trace rather than to genuine reconsolidation of the old one. It will not be further discussed here. The "intermediate" version of the reconsolidation hypothesis claims that upon retrieval the activated trace becomes labile and modifiable, and has to undergo some new process of stabilization. Given the appropriate interference, parts of the trace that were encoded and consolidated in the original experience might become corrupted in the process, either permanently or transiently. This susceptibility to corruption might be the price paid for modifiability. In real life, consolidation blockers are not frequent—we don't usually swallow anisomycin upon recalling our past—so the price might not be too high. In any case, according to this version of the hypothesis, a core of the original trace remains immune to the new wave of consolidation because it is too mature, or is retained in multiple copies, and/or is richly associated with other traces. This version is the one most comfortable to accommodate with the current data and theory. The "strong" version of the reconsolidation hypothesis is, as its name implies, the most radical one. It also assumes, like the intermediate version, that consolidation does not occur just once in the life of the trace, but further posits that the entire trace, including its original parts, becomes labile and potentially disruptable upon activation in retrieval, and could therefore be utterly erased by consolidation blockers. This hypothetical version, which promotes genuine overall reconsolidation of the original consolidated trace, is the major focus of the renewed debate in the neuroscience of memory.

RESERVATIONS CONCERNING THE STRONGER VERSIONS OF THE RECONSOLIDATION HYPOTHESIS

Briefly, the following arguments are or could be raised. They apply to some degree to both the intermediate and the strong hypotheses but in practice focus specifically on the strong hypothesis, which is more provocative. These arguments are based on data cited above, and only the bottom line will be provided in each case.

a. *Apparent inconsistencies in the findings*. These have been sampled above. Most importantly, in some systems, and under certain protocols, the original trace becomes labile to interference upon its activation, in others it's not. In some studies, reconsolidation was observed long after the memory has consolidated, in others, only for a limited period after synaptic consolidation. In some studies, in both the initial and the current wave of research on reconsolidation, the amnesia produced by the postactivation consolidation

blocker was transient, or could be overcome by reinstatement; in others, it persisted throughout the period studied.

b. *The need for more data*. At the time of writing, several notable studies have already been published on reconsolidation, but the body of research as a whole is still relatively modest, some would claim too modest to reach firm conclusions on the boundary conditions and generality of the phenomenon. Particularly noteworthy are two issues. First, laboratories that currently investigate reconsolidation use different systems and protocols. Second, several types of controls, which are highly desirable, are still missing in some studies. Hence the possibility could be raised that after the retrieval experience, a new trace is formed that takes control over behavior, similar to the situation in experimental extinction, in which case reconsolidation effects might actually represent accelerated extinction. This is not a very appealing explanation, because anisomycin blocks consolidation after learning, so why should it accelerate memory after relearning, i.e., experimental extinction? Still, the possibility should be checked. Extinction is characterized by the possibility of spontaneous recovery, saving, reinstatement, and renewal (Dudai 2002a), all of which are amenable to experimental analysis. Such experiments could be useful in probing the possibility that the old trace is only reverted to a latent state.

c. *Lady Macbeth's argument*. Using the original formulation, it goes like this: "What's done cannot be undone." Suppose formation of the engram involves induction of functional and morphological changes in a finite number of synapses at time $t = i$; it is counterintuitive, so goes the argument, to assume that after a long time, a new experience could retrace the former changes and undo them so that the state of these same synapses at time $t = j$ returns to its values at $t = i$. It is in contradiction with what we currently know about the massive turnover of synapses in the mammalian brain and the intricate dynamics of intracellular signal cascades. This argument is discussed below.

d. *Reconsolidation is against the zeitgeist*. This is not really a valid argument, and has nothing to do with how experimental science should be conducted; rather, it is within the domain of the pragmatics and sociology of science. But it does occasionally pop up in discussions, so it should be spelled out.

SELECTED RESPONSES TO THE RESERVATIONS

It is noteworthy that arguments similar to those raised against the stronger versions of the reconsolidation hypothesis were raised several decades ago against the consolidation theory. Prominent among them is the possibility that the amnesia produced is reversible. In many experiments performed in the past 50 years no reversibility of amnesia produced by consolidation blockade has been reported,

and those few cases in which reversibility was observed were either explained (e.g., by dissociation of memory systems) or essentially neglected. It remains to be seen how many laboratories will report irreversibility of amnesia following postreactivation consolidation blockade, in order to determine the majority vote and seek explanations for the exceptions. As to discrepancies in the sensitivity of the original trace to postreactivation interference, as noted above, the shifting identity of the behaviorally dominant trace after retrieval might explain at least some of these. Also, because at the time of writing no lab has yet replicated exactly the same protocol of any other lab in this field, the term "inconsistencies" should be taken with a pinch of salt. And the possibility that a new trace—which somehow blocks the expression of the original trace—is formed in reactivation must still be scrutinized. Of all the criticism briefly cited above, it is the "what's done cannot be undone" that deserves special attention, because it is less dependent on additional experimental data than the other arguments.

ON THE DISTINCTION BETWEEN RECONSOLIDATION AND DECONSOLIDATION

What the proponents of the reversibility argument probably mean is not that an acquired behavior cannot be undone, but rather that reconsolidation is impossible because the hardware modifications that have led to the encoding of the trace and to its persistence over time are unlikely to be undone. Regardless of whether the stronger versions of the reconsolidation hypothesis are factually valid or not, a fallacy is hidden in the above argument. Its resolution requires a clear delineation of levels of function and analysis, and a distinction between reconsolidation and deconsolidation. This argument assumes deconsolidation: that the state of the system at time $t = j$, after reconsolidation has taken place, is restored to the state of the system at $t = i$, before consolidation had been completed. As noted above, it is not only counterintuitive that the nervous system will be able to retrace its long-ago changes for every item in memory and undo them almost instantaneously, it is also unfeasible to expect, based on what we do know about the life of synapses (e.g., Trachtenberg et al. 2002). It is questionable whether many synapses that had been modified in the original consolidation survive to the time of retrieval months or years later. Reconsolidation, if it occurs, cannot be based on deconsolidation at the synaptic hardware level.

Memories, i.e., experience-dependent internal representations (Dudai 1989), are expected to be encoded in the spatiotemporal states of neuronal circuits or populations. Such states are unlikely to correspond to singular configurations of sets of unique individual synapses; at least in the vertebrate brain, it is highly probable that practically equivalent behavioral states could be replicated by the spatiotemporal activity patterns of distributed systems in which individual synapses are interchangeable or could be gracefully degraded. It makes, therefore, more sense

to consider the notion of reconsolidation as referring to functional-state reversal rather than hardware-state reversal. The illusion of the need for hardware-state reversal stems from being entrapped, usually implicitly, in metaphors that portray the structure of items in memory, once formed, as stagnant (Dudai 2002a, Roediger 1980). Stagnation should not be confounded with stability and stability with persistence. We know that physical systems, neural networks included, could endure for long in semistable energy minima and still show much dynamics and flux (Amit 1989). There is nothing inherent in the concept of reconsolidation that contradicts the logic of such systems. Reconsolidation could hence involve undoing the acquired ability to actualize or reconstruct a certain spatiotemporal neuronal state without undoing the old connections that have created this acquired state in the first place. This still involves synaptic plasticity, i.e., alteration of synaptic weights, and even instances of their reversal—but these synapses should not necessarily be expected to be the original synapses, let alone these same synapses retracing their molecular history.[10] Even if the strong version of the reconsolidation hypothesis is proven valid and survives the independent replications and careful controls that its critics, rightly so, demand, the only thing that it will contradict will be the view that consolidation is a singular event in the life of a memory item.

EPILOGUE

The study of consolidation is of great importance in memory research because it bears on cardinal theoretical and practical issues. To start with the latter, it could cast light on the etiology and treatment of amnesia, on pathologies that involve obsessive recollection, on posttraumatic stress disorder, acquired phobia, and additional affective and cognitive disorders. Consider, for example, the possibility that a specific traumatic memory could be erased upon retrieval; this might lead to a treatment for posttraumatic stress disorder, which is a devastating pathology. Furthermore, understanding consolidation might culminate in methods to improve various types of memory, including the acquisition and reacquisition of skill, a process of significant economic value. On the theoretical side, studies of consolidations contribute to our understanding the nature of the trace, its maturation, its persistence, and its retrievability and expression.

The question of what it is that physically persists in long-term memory is fundamental, yet is only infrequently discussed explicitly in the neurobiological literature (Dudai 2002b). It is futile to try to understand consolidation or the possibility of reconsolidation without addressing the issue of persistence. It is noteworthy,

[10]There is a suggestion that synaptic changes may be undone after a long delay, in memory extinction in *Drosophila* (Schwaerzel et al. 2002). In its most parsimonious interpretation, this idea requires the same synapse to survive throughout the life of the memory. It is unlikely to happen in extinction in mammals, which is considered relearning rather than unlearning.

toward that end, to recapitulate some points that were briefly noted, or only alluded to, in this discussion:

- The long-term trace probably persists in a dormant, inactive, representational state until reactivated in retrieval—or possibly also, in a behaviorally opaque manner, in the course of reorganization or maintenance of memory systems. The activation of the trace implies re-creation or reconstruction of a certain spatiotemporal pattern of neuronal activity. The distinction between inactive and active states of the trace deserves more attention than it has so far received since Lewis (1979) explicitly formulated it.
- To persist in a functionally useful manner, the trace must possess not only the ability to re-express the specific internal representation, but also "retrieval handles" that permit activation by some but not other representations. Each act of retrieval might involve the use and use-dependent modification of only part of the set of retrieval handles of that particular representation. The role of consolidation, particularly synaptic consolidation, in establishing and remodeling persistent retrieval handles is mostly a *terra incognita* whose exploration might promote the understanding of postacquisition and postretrieval consolidation.
- At least in the mammalian cortex, the trace is unlikely to persist over prolonged periods by being dependent on the same set of individual synapses that had subserved its encoding. Spatiotemporal patterns of neural population activity, which have a similar mental and behavioral meaning, might be reactivated or reconstructed by nonidentical synaptic ensembles.
- In biological memory systems, persistence should not, therefore, be confounded with structural stability, and stability with stagnation.
- Moreover, modifications in synapses and nerve cells should not be simply equated with modifications in memory. Those are different levels of organization and function, where one level (cellular) is assumed to subserve, by virtue of its plasticity, the other (behavioral), but the translation rules that govern this interaction are not yet known. Further, it is premature to determine whether identified functional or morphological changes in synapses, which are correlated with, and obligatory for, the processes of learning and consolidation, are indeed causally related to the encoding and persistence of memory per se, as opposed to auxiliary processes that are required for the formation of the trace but do not embody it.
- Overall, therefore, consolidation should not be portrayed as freezing of a structural state of the synapse, let alone reconsolidation, if it does exist in its stronger versions, as reversal to the prefrozen physical state. The system is too dynamic to allow such reversal; moreover, it most likely does not require it for replicating or annulling behaviorally meaningful states.

Scientific paradigms might be more static and resistant to change than brains. The current exciting debates in the field of memory consolidation are bound to

culminate in models that will be more faithful to reality. In the meantime, these debates shake the zeitgeist a bit, which can do only good. They also turn our attention to the possibility that when it applies to memory, consolidated memory included, the Greeks got it right again: Everything flows, *Panta Rei*.

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