The Restless Engram: Consolidations Never End

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Annu. Rev. Neurosci. 2012. 35:227–47

First published online as a Review in Advance on March 20, 2012

The *Annual Review of Neuroscience* is online at neuro.annualreviews.org

This article's doi: 10.1146/annurev-neuro-062111-150500

0147-006X/12/0721-0227$20.00

Keywords

memory trace, long-term memory, behavioral plasticity, memory systems, episodic memory, internal representations

Abstract

Memory consolidation is the hypothetical process in which an item in memory is transformed into a long-term form. It is commonly addressed at two complementary levels of description and analysis: the cellular/synaptic level (synaptic consolidation) and the brain systems level (systems consolidation). This article focuses on selected recent advances in consolidation research, including the reconsolidation of long-term memory items, the brain mechanisms of transformation of the content and of cue-dependency of memory items over time, as well as the role of rest and sleep in consolidating and shaping memories. Taken together, the picture that emerges is of dynamic engrams that are formed, modified, and remodified over time at the systems level by using synaptic consolidation mechanisms as subroutines. This implies that, contrary to interpretations that have dominated neuroscience for a while, but similar to long-standing cognitive concepts, consolidation of at least some items in long-term memory may never really come to an end.

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INTRODUCTION

Memory consolidation: hypothetical process in which a memory item is transformed into a long-term or remote form

Those who consider *In principio erat verbum* ("in the beginning there was the word") as a biblical aphorism only, philosophical connotations notwithstanding, may be gratified to discover that it applies to scientific research as well. Occasionally, scientific practice is shaped by terms whose original meaning has mutated over time. The study of memory consolidation provides an intriguing example. Since first proposed by Muller & Pilzecker (1900), the term consolidation has acquired multiple usages and meanings. It even budded off new terminology by acquiring a prefix (reconsolidation). Given the recent impressive advance of research on this topic, it seems apt to explore what memory consolidation currently means and the implications concerning our understating of memory at large.

Imaginative and resourceful as they were, Muller and Pilzecker were not the first to identify consolidation. Roman orators already knew about it (Quintillian 1C AD/1921). Though not yet so termed, consolidation entered the clinical discourse as a consequence of observations of amnesic patients (Ribot 1882). This and additional findings that preceded and coincided with the studies by Muller and Pilzecker are not reiterated here (Dudai 2004). Many impressive advances in molecular, cellular, and systems neuroscience that relate to memory mechanisms are also not discussed. Instead, the present discussion focuses on selected recent developments that have changed our view on how memories become long-term and on their subsequent fate.

CONCEPTS AND CRITERIA

Memory consolidation is the hypothetical process in which a memory item is transformed into a long-term form. It is commonly addressed at two levels of description and analysis: the cellular/synaptic level and the brain systems level. Synaptic consolidation refers to the post-encoding transformation of information into a long-term form at local nodes in the neural circuit that encodes the memory. The current central dogma of synaptic consolidation is that it involves stimulus ("teacher")-induced activation of intracellular signaling cascades, resulting in posttranslational modifications, modulation of gene expression, and synthesis of gene products that alter synaptic efficacy. Synaptic consolidation is traditionally assumed

to draw to a close within hours of its initiation. The stimulus that triggers it in the local node may represent perceptually or internally driven information. Synaptic consolidation is found throughout the animal kingdom.

Systems consolidation refers to the postencoding reorganization of long-term memory (LTM) over distributed brain circuits. The process may last days to years, depending on the memory system, task, and author. The conventional taxonomy of LTM systems (Squire 2004) distinguishes between declarative memory, which is memory for facts (semantic) or events (episodic) that requires conscious awareness for retrieval, and nondeclarative memory, a collection of memory faculties that do not require conscious awareness for retrieval. Systems consolidation commonly refers to declarative memory, but may exist in nondeclarative memory as well.

"Reconsolidation" refers to a consolidation process that is initiated by reactivation of LTM. The process is assumed to transiently destabilize LTM.

How Is Consolidation Identified?

Although certain changes detected in the brain may reflect consolidation, none can so far be used as a definitive signature of consolidation. Currently, the only accepted criterion to infer consolidation is the existence of a time window of susceptibility to amnesic agents. An amnesic agent that does not exhibit time-dependent decrease in efficacy is assumed to affect maintenance or expression of memory rather than consolidation (Shema et al. 2007).

RE-CONSOLIDATION, OR IS IT?

The traditional consolidation hypothesis implied that, for any item in LTM, consolidation starts and ends just once. Accordingly, classical discussions of consolidation referred explicitly to the "fixation" of memory (Glickman 1961, McGaugh 1966). Social psychology and introspection favored a shakier engram (Bartlett 1932), but proponents of the consolidation hypothesis drew a distinction between the postulated immutability of consolidated memory items and the dynamic nature of behavior (McGaugh 1966). The view that consolidation occurs just once per item was, however, challenged by the late 1960s. Researchers reported that presentation of a reminder cue (RC) rendered a seemingly consolidated memory item labile to amnesic agents (Misanin et al. 1968). The prototypical experimental protocol goes like this: Training is followed by time to complete the postulated consolidation period. An RC, usually the conditioned stimulus (CS), is then presented to reactivate the memory. An amnesic agent is administered simultaneously or immediately afterward. LTM is then retested. Under these conditions, LTM may be blocked. No such effect is detected if retrieval is not followed by the amnesic agent or the amnesic agent is not preceded by retrieval. This reactivation-induced reopening of a consolidation-like window challenged the unidirectional memory maturation view (Spear 1973) and was termed reconsolidation (Rodriguez et al. 1993, Przybyslawski & Sara 1997).

Reservations concerning interpretations as well as paradigmatic drives diverted the exploration of reconsolidation away from mainstream memory research. Although a few groups pursued the topic (reviewed in Sara 2000), the notion lost favor, as reflected, for example, in the number of publications: Of the 27,061 papers relating to "memory" published in the psychobiology literature from 1993 to 1999, only 6 referred to "reconsolidation" (*Thomson Reuters Science Web of Knowledge*). The notion of reconsolidation was ultimately revitalized by a study that targeted an identified memory circuit in the brain (basolateral amygdala) and blocked reactivated LTM of a well-defined task (fear conditioning) with a widely used amnesic agent (the protein synthesis inhibitor anisomycin) (Nader et al. 2000). This signal paper triggered a surge of interest, data, and insights. Bibliometry

Synaptic consolidation: hypothetical process in which information is transformed into a long-term form at local nodes in the neural circuits that encode the memory

Systems consolidation: hypothetical process in which an experience-dependent internal representation is converted into a long-term form and reorganized over distributed brain circuits

Reconsolidation: postulated consolidation process initiated by reactivation of a long-term memory item in the system that already stores this item

Long-term memory (LTM): item lasting long after it is encoded; in behavioral neuroscience, "long" is conventionally considered more than one day

Declarative memory: requires conscious awareness for retrieval, usually classified into memory for facts (semantic) and memory for events (episodic)

Nondeclarative memory: can be retrieved in the absence of conscious awareness, for example, habit and skill

Engram: the physical record of a memory item in the brain; a memory trace

RC: reminder cue

CS: conditioned stimulus

US: unconditioned stimulus

again illustrates the trend: From 2001 to 2010, of the 61,950 publications on memory, 413 referred to reconsolidation (*Thomson Reuters Science Web of Knowledge*), presenting an almost 50-fold absolute increase per annum in the scientific vox populi.

Phenomena construed as reconsolidation have now been reported in many species and memory protocols. They were demonstrated mostly in synaptic consolidation but shown to occur also in systems consolidation (Debiec et al. 2002, Winocur et al. 2009). The resurrection of reconsolidation was not greeted smoothly. Reservations were raised once again concerning interpretations (McGaugh 2004). Yet, it soon became a widely accepted and stimulating observation (Dudai 2004, Nader & Hardt 2009, Alberini 2011, McKenzie & Eichenbaum 2011). The present discussion refers to only a few key questions that have gained particular attention as the field has progressed.

Boundary Conditions for Reconsolidation

Reconsolidation seems not to occur every time LTM is reactivated. Understanding the conditions under which it takes place is likely to cast light on storage and retrievability of memory in general. Among the boundary conditions for reconsolidation identified so far, two are noted here. The first relates to competition among memories that are elicited by the RC. The second relates to the role of new information upon presentation of the RC.

When multiple associations are elicited by the RC, the one that comes to dominate behavior tends to reconsolidate (Eisenberg et al. 2003). In most reconsolidation studies, the competing associations are the original CS–unconditioned stimulus (US) association and the "inhibitory" CS–US association (i.e., the outcome of experimental extinction). If one could identify exactly when to intervene with an amnesic agent in the course of retrieval/extinction training, it would be possible to favor or block one of the competing traces. This appears to depend on the task and on the kinetics of RC presentation (Eisenberg et al. 2003, Suzuki et al. 2004, Garelick & Storm 2005, Monfils et al. 2009, Perez-Cuesta & Maldonado 2009, de la Fuente et al. 2011). Yet, this approach has already been reported to allow attenuation of fear memories (Monfils et al. 2009, Schiller et al. 2010) (see below).

Another important boundary condition for reconsolidation is the requirement of novel information at the time of the reactivation session. Studying fear conditioning in the crab *Chasmagnathus*, Pedreira et al. (2004) concluded that impairing reactivated LTM by a protein synthesis inhibitor was effective only when there was a mismatch between what the animal expected and what actually occurred. Such mismatch drives learning (Rescorla & Wagner 1972). Indeed, using spatial memory and intrahippocampal infusions of a protein synthesis inhibitor in the rat, Morris et al. (2006) identified reconsolidation only when the protocol involved encoding of new information at the time of retrieval (see also Rodriguez-Ortiz et al. 2008). Similarly, Winters et al. (2009) reported that, in object recognition in the rat, the N-methyl-D-aspartate (NMDA) glutamate receptor inhibitor blocked reactivated LTM so long as salient novel contextual information was present during memory reactivation. Of relevance is also the observation that blockade of the NMDA receptor, which is critical for encoding, blocked reconsolidation, but not expression, of fear memory in the rat (Ben Mamou et al. 2006). Evidence supporting the importance of encoding in triggering reconsolidation could also be inferred from studies of human procedural (Walker et al. 2003) and declarative (Hupbach et al. 2007, Forcato et al. 2009, Kuhl et al. 2010) memory. All in all, this evidence raises the possibility that reconsolidation has to do with updating old with new information (but see Tronel et al. 2005). The possibility should also not be excluded that the two boundary conditions—trace competition and need for new information—reflect a common basic requirement, as the new information may be considered to compete with the old.

Reconsolidation as an Opportunity for Memory Enhancement

If reconsolidation updates memory, one should also be able to exploit it for reinforcing memory. Indeed, this has been demonstrated by several studies. Tronson et al. (2006) reported that, upon retrieval of long-term fear conditioning in the rat, inhibiting the activity of the enzyme protein kinase A in the amygdala impaired memory, whereas stimulating this enzyme enhanced memory. In humans, it is more practical to use sensory and verbal stimuli instead of pharmacological agents. Coccoz et al. (2011) trained volunteers to associate syllables in a distinct audiovisual context. They reactivated LTM by presenting the training context followed by one of the cue syllables, but instead of getting the opportunity to complete the test, the participants were instructed to immerse their arm in ice-cold water. A day later memory was tested, this time without interruption. The exposure to the stressor upon reactivation of the memory enhanced performance on the subsequent day. Similar results, though taxing shorter-term memory, were reported by Finn & Roediger (2011), this time using pairs of Swahili-English vocabulary words as memoranda and presenting negatively arousing pictures immediately after a cued recall test. Performance on the subsequent recall test was best for items whose initial retrieval was followed by the negative pictures.

Luckily, an arm in ice or annoying pictures are not the only ways to exploit reconsolidation for the sake of improving memory. Both schoolchildren and university students can improve their memory by practicing self-testing, because retrieval practice is a powerful mnemonic enhancer (Karpicke & Roediger 2008). This could well be the contribution of reconsolidation to success in the classroom (Roediger & Butler 2011).

Reconsolidation in the Real World

That some types of memory could be enhanced merely by testing was known before reconsolidation was implicated in the process, and the practical benefit of knowing that reconsolidation is involved is still unclear. Similarly, reconsolidation may help in understanding why episodic information becomes distorted over time (Hupbach et al. 2007, Edelson et al. 2011), but it is unlikely that this understanding could be used to remedy false memory. In contrast, in some other real-life phenomena in which reconsolidation may be involved, understanding the mechanisms may culminate in beneficial interventions. The most salient example concerns the attempt to ameliorate posttraumatic stress disorder. Two approaches are used. In one, investigators administer shortly before, during, or immediately after memory reactivation a drug that suppresses physiological manifestation of emotion. A β-blocker is the drug of choice because of its proven safety. Following this administration, patients with chronic posttraumatic stress disorder had attenuated memory for one day in human eyeblink conditioning to noise (Kindt et al. 2009), emotional enhancement of verbal information (Kroes et al. 2010), and a physiological response associated with imagery of trauma (Pitman et al. 2006). Despite these results, the clinical value of this approach is still unclear.

The other approach is nonpharmacological. Schiller et al. (2010) adapted for humans the procedure devised by Monfils et al. (2009) for the rat. Monfils et al. (2009) conditioned rats to associate tone with shock, and after 24 h, they activated the memory by the tonal CS, followed by extinction training within or after the reconsolidation window, which closes within a few hours. When tested for subsequent LTM, the rats that received extinction training within the reconsolidation window, but not afterward, displayed attenuated conditioned fear 24 h later. There was no reversal of fear as judged by spontaneous recovery, renewal (testing in a different context), reinstatement (retraining on the US only), and saving (amount of training needed for reacquisition of the task after extinction).

Schiller et al. (2010) exploited similarly the extinction-reconsolidation boundaries in humans. They trained participants to fear a

visual CS by associating it with a mild shock to the wrist. A day later they presented the CS only. The participants were then trained in an extinction paradigm after 10 min or 6 h. In the 10-min group, LTM, as expressed in skin conductance response to the CS, was blocked even one year later. It now remains to be seen whether these results hold also for real-life complex recollections. It is not expected to be easy: Even in rats, higher-order associations are not blocked by blocking reconsolidation (Debiec et al. 2006), and resilient real-life traumatic memories in humans are expected to be densely associated. Nevertheless, the approach provides hope for treatment.

Can blockade of reconsolidation erase memory, or just block its expression? The tools available to assess memory erasure in reconsolidation are identical to those used in the study of extinction and consolidation. The gold standard is the lack of spontaneous recovery, reinstatement, renewal, and saving. Hence, demonstrating that the defect is a storage rather than a retrieval impairment relies on a negative finding: Memory not found, ergo memory not there. To circumvent the problem, researchers need new methods so they can identify the neuronal signature of the distinct engram (Nader & Hardt 2009).

Are Consolidation and Reconsolidation the Same?

The types of neuronal mechanisms that subserve reconsolidation are basically similar to those that subserve consolidation. First and foremost, inhibitors of macromolecular synthesis block both processes (Nader et al. 2000). Differential contributions of a spectrum of receptors, intracellular signaling, and transcription factors to reconsolidation versus consolidation have, however, been described. Examples of these differences include the obligatory involvement of brain-derived neurotrophic factor, but not the transcription factor Zif268, in consolidation and vice versa in reconsolidation of contextual fear memory in the rat hippocampus (Lee et al. 2004); the recruitment in reconsolidation of only a subset of immediate-early genes that are induced in consolidation (von Hertzen & Giese 2005); and the requirement for the interaction between specific initiation factors in the lateral amygdala in consolidation but not reconsolidation of elemental fear conditioning in the rat (Hoeffer et al. 2011). It remains to be determined whether a differential contribution to reconsolidation could be identified in mechanisms that have recently gained increased attention in consolidation research, such as additional growth factors (Chen et al. 2011), protein degradation (Lee et al. 2008), and epigenesis (Day & Sweatt 2011).

The question arises, however, whether the molecular dissociations, once found, reflect a fundamental dissociation between consolidation and reconsolidation. Differences in the contribution of specific molecular components to encoding, extinction, or reconsolidation can stem from differences in cue valence, context, or test demands (Berman & Dudai 2001, Tronson & Taylor 2007). This probably accounts for the lack in generalization of molecular signatures across reconsolidation tasks (Tronson & Taylor 2007). Hence, even if some differences are identified in the molecular signatures of consolidation and reconsolidation, the question remains whether they reflect genuine mechanistic differences that warrant proclaiming these as distinct natural kinds. The suggestion was, therefore, made that reconsolidation is use-dependent lingering consolidation, whose function is to update learned information (Dudai & Eisenberg 2004, Alberini 2005, McKenzie & Eichenbaum 2011). In that case, it might pay off to stop updating information about events that do not significantly change or such that lose their relevance. This might happen in some cases as memory ages (Milekic & Alberini 2002, Eisenberg & Dudai 2004, Inda et al. 2011).

THE ENGRAM TRANSFORMED

If reconsolidation is lingering consolidation, it brings us already into the time domain of

systems consolidation. Evidence for systems consolidation stems from both human (clinical and neuropsychological) and animal research (Dudai 2004, Squire 2004, Frankland & Bontempi 2005, Wang & Morris 2010, Winocur et al. 2010, McKenzie & Eichenbaum 2011). In line with the early clinical observations that contributed to the emergence of the consolidation hypothesis (Ribot 1882, Burnham 1903), a substantial number of studies report that "global" amnesics, i.e., patients with damage in their medial temporal lobe (MTL), displayed temporally graded retrograde amnesia on declarative memory tasks. The type of memory tested, whether episodic or semantic, is highly relevant, as explained below. In addition, a substantial number of studies using animal models of amnesia confirm that the hippocampus is required for LTM for only a limited time after encoding (Squire et al. 2001; for studies with differing conclusions, see Winocur et al. 2010, Sutherland & Lehmann 2011). In addition, a substantial number of functional brain imaging studies in healthy human participants show reduced recollection-correlated activity over time in mediotemporal structures but increased activity in the neocortex (e.g., Smith & Squire 2009; see also Smith et al. 2010). Similar conclusions emerge from metabolic mapping in laboratory animals (Bontempi et al. 1999, Ross & Eichenbaum 2006).

The Standard Model of Systems Consolidation

A dominant model that attempted to explain graded retrograde amnesia was the standard consolidation theory (SCT) (McClelland et al. 1995, Squire 2004; for an influential harbinger, see Marr 1971). This model posits that the hippocampus is only a temporary repository for memory and that the neocortex stores the memory thereafter. Specifically, the model postulates that encoding, storage, and retrieval of declarative information is initially dependent on the hippocampal complex (HPC) and related MTL structures as well as neocortical areas relevant to the encoded stimuli. The hippocampal trace is probably a compressed version of the representation. Over time, the information reorganizes by replaying (see below) the hippocampal representation to the neocortex. This reinstates the corresponding neocortical memory, resulting in incremental adjustments of neocortical connections and establishment of a long-lasting, reorganized representation, while the hippocampal memory decays.

SCT: standard consolidation theory

HPC: hippocampal complex

MTT: multiple-trace theory

The Multiple-Trace and the Trace-Transformation Models

Over time, some evidence that seems incompatible with SCT has accumulated. Most significant, the effect of MTL lesions on subtypes of declarative memory is not consistent: Autobiographical episodes are the most severely affected, and the retrograde temporal gradient for this type of memory is either absent or very shallow, sparing only memories acquired several decades earlier. Driven by these observations and corresponding findings in animal models of amnesia, Nadel & Moscovitch (1997) proposed an alternative, the multiple-trace theory (MTT). MTT posits that the HPC rapidly and obligatorily encodes all episodic information. This information is sparsely encoded in distributed ensembles of HPC neurons, acts as an index for neurocortical neurons that attend the information, and binds them into a coherent representation. The resulting hippocampal-neocortical ensemble constitutes the memory trace for the episode. Because reactivation of the trace commonly occurs in an altered context, it results in newly encoded hippocampal traces, which, in turn, bind new traces in the neocortex. This results in multiple traces that share some or all the information about the initial episode. Over time, having multiple related traces facilitates the extraction of factual information into a semantic representation of the gist of the episode. This information integrates into a larger body of semantic knowledge and becomes independent of the specific episode. Contextual information about the episode, which is required for bona fide episodic recollection, continues,

Remote memory: lasts longer than a few months (in animals) to many years (in humans)

TTT: trace-transformation theory

SAM: schema assimilation model

however, to depend on the HPC as long as the memory exists. Opponents to MTT claimed that patients with well-characterized MTL lesions show intact remote, including autobiographical, memory, unless the damage exceeds the MTL (Squire & Bayley 2007). This argument has been challenged (Rosenbaum et al. 2008, Race et al. 2011). It also does not explain why functional neuroimaging identifies in healthy individuals HPC activation in retrieval of remote autobiographical memory (Gilboa et al. 2004, Viard et al. 2010). Among the open questions concerning the functional imaging data are the following: To what extent do cue-induced imagining processes (Hassabis et al. 2007), as opposed to genuine recollection, contribute to HPC activation? Does this activation reflect processes essential for, or just correlative to, retrieval?

An update of MTT, the trace-transformation theory (TTT), focuses on the proposed abstraction and transformation of HPC-neocortical episodic information into neocortical semantic representations (Winocur et al. 2010, Winocur & Moscovitch 2011). The resulting gist memories are posited to coexist and interact with those representations in which the context/episodicity is retained and that remain HPC dependent. Winocur et al. (2007) tested a TTT prediction in the rat by using context-dependent versions of two hippocampal-dependent tasks—peer-induced food preference and contextual fear conditioning. They tested the rats at short and long intervals in the training context or in a different context. According to TTT, but not according to a conservative reading of SCT (which predicts that HPC memories are reorganized in a similar form in the neocortex), the change in context is expected to affect performance at the short but not the long interval when the contextless schematic version of the memory is supposed to take over. This indeed was the case.

The Schema Assimilation Model

SCT and MTT consider systems consolidation as a gradual, lengthy process. The schema assimilation model (SAM) (Tse et al. 2007) posits that systems consolidation could be accomplished quickly if a previously established body of related knowledge, i.e., a mental schema (Bartlett 1932), is available into which the new knowledge may be assimilated. Tse et al. (2007) trained rats using hippocampal-dependent flavor-location associations. After the rats learned a set of different associations over a few weeks, a single trial learning was sufficient to consolidate rapidly the memory of a new association: Although hippocampal lesion 3 h after training disrupted subsequent LTM, a similar lesion at 48 h was ineffective, demonstrating that LTM was no longer hippocampal dependent. No such effect was seen when the rats were trained with inconsistent flavor-location-paired associates, indicating that formation of a postulated schema is a prerequisite for rapid systems consolidation. The rapid schema–dependent learning was associated with upregulation of immediate-early genes in the medial prefrontal cortex (Tse et al. 2011), whereas pharmacological intervention targeted at that area prevented the new learning as well as the recall of consolidated information. These findings are in agreement with the assertion of earlier models that initial memory is in both the HPC and the neocortex (see also Lesburgueres et al. 2011), but they are in disagreement with the assumption that the neocortex is a slow learner (on additional evidence for fast cortical learning, see Takashima et al. 2009; on sleep and consolidation, see below).

That different systems consolidation models coexist is a stimulating situation, as they provide opportunities for new hypothesis-driven experiments, which are likely to generate not only new data but also new models.

WORKING AT REST

Synaptic consolidation processes take place immediately after encoding and re-encoding. But when does systems consolidation happen? Apparently some of the action takes place when we rest and while we sleep. The contribution of rest and sleep to consolidation is one of the

most fascinating frontiers in current consolidation research.

The idea that sleep enhances memory predates scientific investigation. Quintillian (1C AD/1921) turns his readers' attention to the "curious fact. . .that the interval of a single night will greatly increase the strength of the memory." It took some time for scientific research to reconfirm that this is the case (Jenkins & Dallenbach 1924). Systematic analyses of sleep and brain mechanisms followed with the development of functional brain-imaging techniques (Smith & Butler 1982, Karni et al. 1994). Ample evidence now supports the claim that memory consolidation benefits from sleep (Stickgold & Walker 2007, Diekelmann & Born 2010a; for a dissident view, see Vertes & Siegel 2005). However, questions arise regarding which (type of) memory, which (process of) consolidation, and which (mechanism of) sleep are involved.

A Reminder Concerning Sleep

Sleep is a natural, reversible physiological and mental state characterized by reduced consciousness, suspended volitional sensorimotor activity, and altered metabolism (Steriade & McCarley 2005). It involves the cyclic occurrence of phases, each conventionally defined by characteristic differences in brain activity, coordinated eye movements, and tonic muscle activity. The standard classification of sleep in primates and felines is into rapid eye movement (REM) and non-REM (NREM) stages. In humans, they alternate roughly every 90 min. NREM is further divided into substages, corresponding to the depth of sleep. NREM stage N3 (formerly stages 3 and 4), in which the deepest sleep occurs, is referred to as electroencephalogram (EEG) slow-wave sleep (SWS) based on the prevalence of EEG slow waves (below 4Hz). Other types of field-potential oscillations that characterize SWS include "spindles" (0.5–2 s, 10–15 Hz) and transient, sharp-wave "ripples" (SWR) (50–120 ms, 100–250 HZ). SWR probably reflect a transient relief of inhibition, permitting windows of opportunity for the expression of selective representations (Csicsvari et al. 1999). REM sleep is characterized by ponto-geniculo-occiptal waves and theta activity (approximately 4–7 Hz). REM and NREM also differ markedly in the level of activity of neuromodulatory systems in the brain during each of the phases (Pace-Schott & Hobosn 2002). SWS appears mostly in early sleep, whereas REM sleep occurs mostly at late sleep. Dreams, the succession of sensorimotor and affective hallucinatory experiences that occur involuntarily during sleep, are prevalent during REM but not confined to it (Nielsen 2000, Nir & Tononi 2010).

SWS: slow-wave sleep

SWR: sharp-wave "ripples"

REM: rapid eye movement

NREM: non-REM

Which Memory Systems Benefit from Consolidation in Sleep?

The evidence for the role of sleep in consolidation of acquired sensory and motor skills was initially considered more robust than that for other types of memory (Walker & Stickgold 2004). A wide spectrum of skills have been studied in this respect (Karni et al. 1994, Walker et al. 2005, Ferrara et al. 2008, Mednick et al. 2009, Wamsley et al. 2010a). It is now well established, however, that declarative memory benefits from sleep as well, though the involvement and contribution of distinct sleep stages and the underlying brain mechanisms to declarative and nondeclarative memory may differ (Diekelmann & Born 2010a,b; Walker & Stickgold 2010; also see below). A broad spectrum of tasks that involve declarative components or are considered "classical" declarative tasks have been investigated (Fenn et al. 2003, Wagner et al. 2004, Sterpenich et al. 2009, Diekelmann et al. 2011, Rauchs et al. 2011, Wilhelm et al. 2011).

Which Properties of Memory Increase the Benefit from Consolidation in Sleep?

Sleep may promote the preferential strengthening of emotional memoranda (Sterpenich et al. 2009) and of items that are expected to be subsequently retrieved (Rauchs et al. 2011, Wilhelm et al. 2011). The possibility that

consolidation in sleep favors selected items gains support from multiple lines of evidence. Rudoy et al. (2009) trained awake participants to associate object locations with sound and found that only those associations that were cued during sleep with their relevant sound were strengthened. This was taken to indicate that specific associations are preferentially reactivated and strengthened during sleep. At the brain physiology level, Huber et al. (2004) reported that activity in SWS has a local component that can be triggered by a sensorimotor adaptation task that involves specific brain regions. Additional electrophysiological evidence shows that most sleep slow waves and their underlying neuronal states occur locally in the brain and, hence, are fit to process information selectively (Nir et al. 2011).

When and How in Sleep

An early report on the role of sleep in consolidation of perceptual skill suggested that REM sleep is critical (Karni et al. 1994). Furthermore, a brief nap was reported to be effective in off-line improvement of skill performance only when the nap contained both REM and SWS but not when it involved only SWS (Mednick et al. 2003). The role of REM and NREM in the effect of napping on other types of tasks that involve skill components is task dependent (Korman et al. 2007, Wamsley et al. 2010b). The possibility was also raised that, at least in some motor skills, siesta-induced improvement is not due to napping but to resting (Rieth et al. 2010). Additional studies proposed a role in skill consolidation for both REM and NREM stages (Stickgold et al. 2000). Two types of processes have been proposed: stabilization against interference and gain in performance. The suggestion was further made that stabilization benefits from the SWS stage, whereas enhancement benefits from the REM stage (Sagi 2011). However, whether skill consolidation in sleep involves enhancement in addition to stabilization remains unclear (Brawn et al. 2010).

A signal set of findings that paved the way to the exploration of the neuronal and circuit mechanisms involved in memory consolidation at large was that hippocampal place cells (Pavlides & Winson 1989) and place-cell ensembles (Wilson & McNaughton 1994), postulated to encode place representations, "replay" during sleep periods that follow performance on spatial behavioral tasks. The order of firing in the task is largely preserved in the replay (Skaggs & McNaughton 1996). Most studies reported that the replay occurred during SWS, particularly during SWR (Nadasdy et al. 1999, Lee & Wilson 2002, Diba & Buzsaki 2007, Ji & Wilson 2007). The reactivation of hippocampal maps during post-training rest/sleep periods was further reported to predict performance on hippocampal-dependent matching-to-place reward tasks (Dupret et al. 2010). SWR are associated with increased cortico-hippocampal communication (Siapas & Wilson 1998). Indeed replay in SWS was found in the neocortex (Ji & Wilson 2007, Euston et al. 2007, Payrache et al. 2009), but also in the ventral striatum (Lansink et al. 2009). The presumed "reading out" in the SWR is accompanied by compression of the replay (Nadasdy et al. 1999, Euston et al. 2007, Ji & Wilson 2007); in other words, the postulated representation is played in "fast forward" (and, as noted below, under certain circumstances in "fast backward"). The virtual speed is 15–20 times faster than in the real world (Davidson et al. 2009). Replay in REM was also reported during periods of theta modulation with a "read-out" rate close to real time (Louie & Wilson 2001).

However, most importantly, structured replay of hippocampal place cells preserving information on the distinct behavioral experience was found to also occur in the awake state. Such replay is observed time locked either to an immediate experience (Foster & Wilson 2006, Csicsvari et al. 2007, Diba & Buzsaki 2007) or to a spatially and temporally remote one (Davidson et al. 2009, Karlsson & Frank 2009). What happens in sleep may, thus, cast light on the processes and mechanisms that relate

to consolidation in the awake state as well. The replay in the awake state is either forward or backward. For example, Foster & Wilson (2006) reported sequential reverse replay during awake periods immediately after a run on a track, when the rat pauses, with the reverse replay declining with familiarity, whereas Diba & Buzsaki (2007) reported forward replay at the beginning of such a run, as if in anticipation of the run, but reverse replay at the end of the run. Moreover, Dragoi & Tonegawa (2011) reported that some of the replays in aware-rest states are "preplays," i.e., sequences that match those subsequently recorded when the rats were running in a new place. The potential implications of this finding are discussed below.

A single SWR is brief, allowing replay of only a limited distance (approximately 1–2-m run), which fits routine laboratory mazes but not the real life of a wild rat. How does the brain replay realistic distances? It appears that firing sequences corresponding to long runs through a large environment are replayed in chains of shorter subsequences, with each segment corresponding to a single SWR (Davidson et al. 2009).

All in all, it has been proposed that: (*a*) Forward replay during "gaps" in the behavioral performance subserves the retrieval of path information to aid memory-guided decision making; (*b*) postexperience forward replay in both awake and sleep states is likely to subserve consolidation of acquired representations; and (*c*) reverse replay in the awake state may subserve episodic binding (Carr et al. 2011). Thus, once the episode is bound and familiar, additional fast-backward replay may not be needed (see above). Interestingly, echoing the latter proposal, human functional brain imaging in a realistic episodic task revealed immediate (within seconds) poststimulus activity in the hippocampus and in the dorsal striatum that predicted subsequent memory performance. This off-line activity may reflect episodic binding and initiation of consolidation (Ben-Yakov & Dudai 2011). Tambini et al. (2010) reported memory-related enhanced corticohippocampal functional connectivity in rest periods spanning minutes after associative encoding sessions. It is also noteworthy that reactivation of memory during waking and sleep may have different roles and outcomes concerning long-term trace stability. Hence, Diekelmann et al. (2011) reported that reactivation of object-location associations by odor cues during waking resulted in destabilization of the trace, but in SWS it resulted in fast stabilization.

The aforementioned studies potentially implicate replay in memory consolidation by way of correlation (though admittedly, only some of these studies actually correlated replay with subsequent memory). Yet interventional methods suggest a causal link as well. Girardeau et al. (2009) and Ego-Stengel & Wilson (2010) stimulated the hippocampus to selectively disrupt SWR activity in maze-trained rats. They found that disruption during post-training rest periods that included sleep impaired improvement of performance over days of training. This was taken to imply that ripple-related activity could be required for uninterrupted memory consolidation. Of further relevance, disruption of sleep continuity in the mouse by optogenetic stimulation of hypocertin/orexin neurons in the lateral hypothalamus, thereby promoting arousal, impaired later performance on novel object recognition. This was correlated with fragmentation of NREM sleep; the minimal time for uninterrupted sleep critical for consolidation on the task was estimated to be 60–120 s (Rolls et al. 2011). Although no effect on distinct representations or firing patterns was determined, these findings indicate a novel approach to the dissection of consolidation processes at large. They also strengthen the notion that sleep may be not only a correlate, but also a necessary mechanism for proper consolidation.

A few cautionary remarks are necessary. First, because replay is not unique to sleep, any unique contribution sleep provides to consolidation cannot be accounted for solely by replay. If replay in sleep has any specific contribution, it must be considered in combination with other features of sleep, such as the unique metabolic

ACSH: active consolidation in sleep hypothesis

and neuromodulatory milieu and their relevant signaling cascades (e.g., Aton et al. 2009). Thus, whatever we learn from replay in sleep could inform us about consolidation in the awake state as well.

Second, the relevance of the laboratory protocols to real life raises some issues. Many of the aforementioned protocols use task repetition and, hence, heavily tax procedures and learning sets. By contrast, realistic episodic memory is a single trial involving novelty. In this context it is worthy to reiterate that encounter with novel memoranda seems to modify the pattern of replay (Foster & Wilson 2006, Dragoi & Tonegawa 2011).

Third, and probably the most relevant question at this point in time, is whether replay is indeed specifically instrumental in consolidation. Replay may be a signature of a more global information-processing mechanism, in which case, it may be permissive but not sufficient for consolidation.

As noted above, replay is not a simple function of experience (Gupta et al. 2010, Dragoi & Tonegawa 2011). Given this, it is tempting to raise the possibility that what is played, replayed, or preplayed are combinatorial internal representations that could serve as raw material for perceiving, anticipating, reacting, recollecting, and planning. Such representations are likely to gain more visibility in sleep because of the decrease in volitional activity. Linked to a broader conceptual level, this points to the potential role of cue-invoked selection of "prerepresentations" as a Darwinian mechanism in the operation of the mind (Young 1979, Heidmann et al. 1984, Dudai 2002). Seen that way, consolidation, similar to development, perception, and retrieval, involves pruning and selecting information about the world.

How It Might Work

With the above in mind, we now consider models of how consolidation could occur in sleep. To do so, it is useful to note the postulated goals of sleep. An influential overall idea is that sleep evolved to maintain homeostasis (Crick & Mitchison 1983, Borbely & Achermann 1999, Tononi & Cirelli 2006). A specific version of this idea was developed by Tononi & Cirelli (2006). They suggest that plastic processes during wakefulness result in a net widespread increase in synaptic strength in the brain and the role of sleep is to downscale synaptic strength to a baseline level that is energetically sustainable and possibly also more useful for new learning the next day. They further propose that this function is achieved during SWS. This means that sleep plays a necessary role in sustaining memory systems, and is at least permissive yet not necessarily instrumental, let alone sufficient, for consolidation. However, as research proceeds, instrumentality may be unveiled. For example, increasing the signal-to-noise ratio of privileged representations may drive them to consolidate effectively.

A different idea is that sleep involves active processes that consolidate memory, and is hence necessary and instrumental, and possibly also sufficient, in implementing steps in consolidation. This is the "active consolidation in sleep hypothesis" (ACSH) (Diekelmann & Born 2010a). ACSH could be considered an extension of the SCT that posits that declarative memory involves initial storage in the cortico-hippocampal system (step 1), but over time, via representational replay, gets reinstated in the neocortex (step 2). ACSH adds that step 2 benefits from sleep (Diekelmann & Born 2010a). ACSH gains support from additional developments in computational models (Kali & Dayan 2004), though these models do not specify sleep per se as obligatory in implementing the stages proposed.

Diekelmann & Born (2010a) suggest how ACSH may be implemented in the brain. They draw on the sequential hypothesis of sleep proposed by Giuditta et al. (1995), among others. The sequential hypothesis proposes that information acquired during the waking period is processed first in the early sleep stages, NREM and particularly SWS. Subsequent processing occurs in the later sleep stage, REM, and information eventually emerges in a new form upon awakening. Diekelmann & Born (2010a)

propose specifically that, during SWS, slow oscillations, spindles, SWR, and low cholinergic activity all coordinate to promote the reactivation and redistribution of hippocampal-dependent memories to the neocortex, thereby instantiating system consolidation. Subsequently, during REM sleep, high cholinergic and theta activity promote synaptic consolidation of the newly redistributed representations in the neocortex. Ultimately, the individual wakes up with a consolidated memory. Similar systems-synaptic sequences may take place in certain nondeclarative memories as well (Dudai 2004). This type of model is agnostic to the specific systems consolidation models discussed above.

Despite their differences, the aforementioned "homeostatic" and "active" accounts of sleep are not mutually exclusive. Whereas the former emphasizes the function of sleep in general, the latter focuses on its role in consolidation. The evolution of sleep may have been initially driven by homeostatic pressure and active consolidation became nested into it over time. Furthermore, consolidation may have evolved to comply with homeostatic needs (Fischer et al. 2005). In addition, when discussing these models, the possibility should not be neglected that we may be entrapped by an adaptationist philosophy. The mechanisms discussed may have evolved as a by-product of inherent structural and functional constraints of biological systems and not under the selective pressures we contemplate (Gould & Lewontin 1979). Analysis of this possibility, which applies to many models in biology, exceeds the scope of this discussion.

CONSOLIDATIONS INTEGRATED

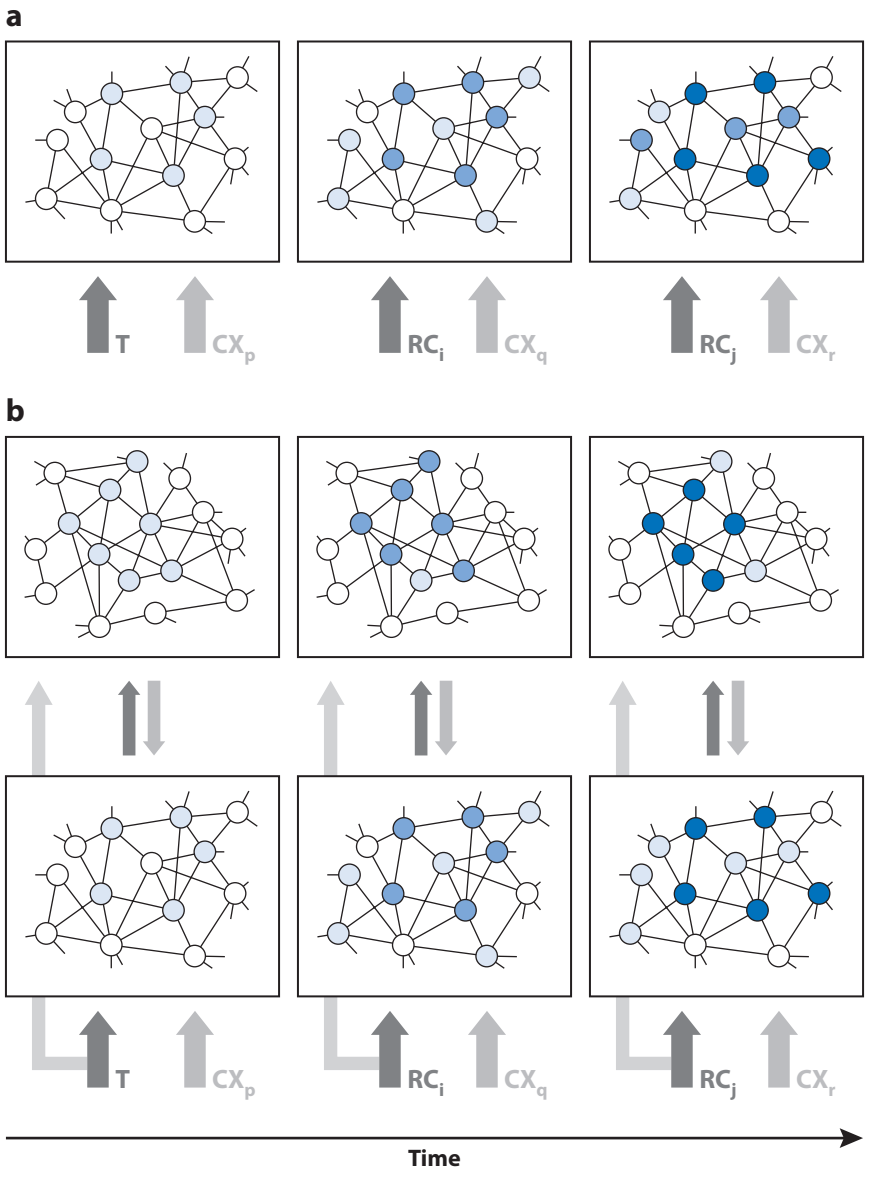
Memory is the retention over time of experience-dependent internal representations or of the informational capacity to reactivate or reconstruct such representations (Dudai 2002). Consolidation is the mechanism that shifts these representations into a long-term form. In considering how this is achieved, three questions are particularly relevant. First, which level of organization of the neural system is critical for encoding the content of the distinct representation? Second, is the circuit that initially encodes the representation also the one that maintains it over time? Third, how does the system ensure that the acquired representation is updated when the world changes?

The assumption that the content of a memory item is encoded at the circuit level is not a secured given, yet is highly reasonable (Dudai 2002). Furthermore, at least in complex memory systems in the mammalian brain, the neural system that encodes the information in the first place may not be identical to the system that stores the information later on, therefore trace migration occurs (McClelland et al. 1995). Given that, an integrative broad-brush depiction of consolidation considers synaptic consolidation as the elementary mechanistic process that converts experience-dependent synaptic change into a longer-term representation. If a mismatch develops between this representation and reality, new information will modify either new or old synapses in the circuit, again by triggering synaptic consolidation. The latter, thus, functions as a subroutine activated once the external and internal cues favor off-line persistence of the change. When this change applies to information already encoded as LTM, we dub it reconsolidation.

In reality, relevant information probably pre-exists in the brain; therefore, even what we deem in the laboratory as consolidation may involve reconsolidation. In memory systems in which information migrates to other distributed brain circuits to free neuronal space and/or distill information into new forms, synaptic consolidation remains the elementary subroutine that executes the process, modifying synapses as they receive new information from other circuits that previously encoded or processed relevant information (**Figure 1**). Seen this way, synaptic consolidation is a local process indifferent to the representational semantics and activated in a similar way regardless of whether the information originated

in the perceptual apparatus or in mnemonic circuits.

Consolidations all have the same computational goal—to allow the adequate level of persistence in the face of expected change (Dudai 2009). Synaptic consolidation is the term we assign to the manifestation of the process at the cellular, elementary "syntactic" level, whereas systems consolidation refers to the circuit, representational "semantic" level. Synaptic consolidation is the basic building block of systems consolidation. In simple systems, the goal of systems consolidation is achieved within the same circuit that first encoded the memory; therefore, we do not see the waves of change in which information redistributes among



circuits. However, local migrations may still occur within the original circuit. It is all a matter of resolution.

ON THE RECONSOLIDATION OF TERMS AND IDEAS

Overall, the evidence discussed in this article suggests that consolidation of information in the behaving brain rarely stops unless one or possibly two conditions occur. Either the behavior and the context in which it is executed remain constant, there is no new information, and therefore no need to learn and update; this probably never happens even in simple systems living in boring environments, but even then, the capacity to update must remain viable. Or, alternatively, the internal representations become highly irrelevant to behavior and therefore not reactivated.

Because knowledge is always based on previous knowledge, and echoing the preamble to this chapter, it might be proper at this point to reactivate the methodology of the Vico (1710), the Italian philosopher who trusted that much can be learned about a culture from the etymology of words used. "Consolidation" is from the Latin *consolidare*, *con-* "together", *solidare* "make firm." The process that we term consolidation in memory research indeed subserves the binding together of acquired information into useful representations, but that information is evidently far from becoming solid. Shortly after the term was first introduced into memory research, emphasis was placed on the *solidare*, and as the term consolidated into the language of the science of memory, that connotation became widespread and guided research to look for stabilization mechanisms. Research in recent years has reconsolidated the connotation of the term to emphasize the inherent malleability of memories. In doing so, the neuroscience of memory reconciles with the intuitive, dynamic view of memory that dominates the cognitive sciences.

Figure 1

Schematic variants of memory consolidation. (*a*) Long-term memory (LTM) is stored in the same circuit, or in parts of the circuit, that initially encoded the memory. The "teacher" stimulus (T) triggers a set of intracellular signaling mechanisms that culminate in long-term alterations (depicted as changes in color) in the efficacy of a set of synapses that subserve encoding of the internal representation. This time-limited process, which is assumed to mature within hours, is termed synaptic consolidation and is an obligatory step in the neural registration of any type of LTM. Reactivation of the LTM by a reminder cue ($RC_{i,j}$) that is associated with new information (e.g., change in context, $CX_{q,r}$) re-triggers synaptic consolidation mechanisms in the same and in additional nodes in the circuit, resulting in synaptic alteration. This is termed reconsolidation and involves some transient destabilization of the original trace. In real life, even the initial consolidation may involve reconsolidation of previous knowledge; in which case, the differentiation between T and RC is not absolute. (*b*) LTM redistributes into new brain territories. The information is encoded first in one location (*lower panel*) and/or in parallel in both locations (*lower and upper panels*). Over time, it migrates, at least in part, from one location to another while probably undergoing metamorphosis in content and cue dependency. The potential direct input of $CX_{p,q}$ to the upstream location has been omitted for simplicity. In each of the locations, the process is executed by synaptic consolidation, whereas T/RC/CX each encodes either sensory and modulatory input (as shown in panel *a*) or information about the item already processed in LTM, manipulated in the absence or in the presence of overt retrieval. This overall process is termed systems consolidation. Hence systems consolidation recurrently recruits synaptic consolidation processes as subroutines. Systems consolidation, which matures within days (or nights) to months or even longer, traditionally deals with the transformation over time of declarative memory in the corticohippocampal system. Processes similar in nature may, however, operate in other memory and brain systems, including in distributed local circuits within the same brain region. For further details, see text. The time arrow is indicated only for the slower, horizontal axis for simplicity.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

I am grateful to Aya Ben-Yakov, Bartosz Brozek, Micah Edelson, Avi Mendelsohn, Morris Moscovitch, Yuval Nir, Matthew Wilson, and Gordon Winocur for comments and discussions.

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