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The Consolidation and Transformation of Memory

Yadin Dudai,[1,2,*] Avi Karni,[3] and Jan Born[4,*]
[1]Department of Neurobiology, Weizmann Institute of Science, Rehovot 76100, Israel
[2]Center for Neural Science, New York University, New York, NY 10003, USA
[3]Sagol Department of Neurobiology and Department of Human Biology, University of Haifa, Mount Carmel 31905, Israel
[4]Center of Integrative Neuroscience and Institute of Medical Psychology and Behavioral Neurobiology, University of Tuebingen, 72076 Tuebingen, Germany
*Correspondence: yadin.dudai@weizmann.ac.il (Y.D.), jan.born@uni-tuebingen.de (J.B.)
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Memory consolidation refers to the transformation over time of experience-dependent internal representations and their neurobiological underpinnings. The process is assumed to be embodied in synaptic and cellular modifications at brain circuits in which the memory is initially encoded and to proceed by recurrent reactivations, both during wakefulness and during sleep, culminating in the distribution of information to additional locales and integration of new information into existing knowledge. We present snapshots of our current knowledge and gaps in knowledge concerning the progress of consolidation over time and the cognitive architecture that supports it and shapes our long-term memories.

Introduction

That the transformation of short-term into longer term memory is not instantaneous was known long before the scientific era, as epitomized in the observation of the Roman orator Quintilian: "… curious fact … that the interval of a single night will greatly increase the strength of the memory … the power of recollection … undergoes a process of ripening and maturing during the time which intervenes" (Quintilian, *Inst. Orat.* 11.2.43, trans. Butler, 1921). Current students of the role of sleep in memory could not agree more. This hypothetical mnemonic maturation process, critical to understanding memory persistence at large, was dubbed two millennia later as "memory consolidation" (Muller and Pilzecker, 1900; see McGaugh, 2000 and Dudai, 2004 for review). However, the concept of consolidation and our knowledge of its biological underpinnings have themselves undergone a long, winding, and sometimes rather surprising process of consolidation and reconsolidation, and recent years have particularly contributed to the elucidation of the brain processes and mechanisms involved. Here, we briefly refer to selected lines of research and attempt to identify emerging conclusions as well as open questions.

Consolidation is commonly addressed at two levels of description and analysis, the cellular/synaptic level and the brain systems level (Box 1). "Synaptic consolidation" (also cellular consolidation, local consolidation) refers to the post-encoding transformation of information into a long-term form at local synaptic and cellular 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 postranslational 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, at the end of which it becomes resistant to a number of agents that otherwise can prevent the memory from being converted into the long-term form ("amnesic agents," among them distracting stimuli and pharmacological agents). Synaptic consolidation exists throughout the animal kingdom. The aforementioned synaptic consolidation type of model emerged from molecular, cellular, and physiological investigation in both invertebrates (e.g., *Aplysia*) and vertebrates (e.g., mice) and has been extensively reviewed (e.g., Kandel et al., 2014), although not without the key role of synapses in consolidation being occasionally challenged (Chen et al., 2014; see also Gallistel and Matzel, 2013 for critique of the relevance of synaptic plasticity to learning and memory in general). We will not further discuss the mechanisms of synaptic consolidation, en passant mentions notwithstanding, and will rather focus on consolidation as observed from the vantage point of the systems level.

"Systems consolidation" refers to the post-encoding time-dependent reorganization of long-term memory (LTM) representations over distributed brain circuits (Dudai and Morris, 2000). It is assumed that systems consolidation involves recurrent waves of synaptic consolidation in the new brain locales that receive new or reprocessed experience-dependent information, i.e., synaptic consolidation could be regarded as subroutines in systems consolidation (Dudai, 2012). Systems consolidation may last days to months and even years, depending on the memory system and the task. The conventional taxonomy of LTM systems (Squire, 2004) distinguishes between declarative memory, which is memory for facts (semantic) or events (episodic) that requires explicit awareness for retrieval, and non-declarative memory, a collection of memory faculties that do not require such awareness for retrieval. Systems consolidation commonly refers to declarative memory and was originally inferred from reports of declining sensitivity over time of declarative memory to hippocampal damage. It was proposed, however, to exist in non-declarative memory as well (see below).

The traditional consolidation hypothesis, whether referring to the synaptic or the systems level, implied that for any item in LTM, consolidation starts and ends just once (reviewed in Dudai, 2004). This view was challenged already in the late 1960s, based on reports that presentation of a "reminder cue" rendered a seemingly consolidated memory item again labile to "amnesic

Box 1. Current Status of the Field

- Memory consolidation is a hypothetical family of processes that take place both during wakefulness and during sleep at multiple levels of organization and function in the brain, from the molecular to the behavioral, and over a temporal spectrum ranging from seconds to months and years. The relatively fast molecular, synaptic, and cellular local mechanisms likely serve as repetitive subroutines in the mechanisms that embody slower systems consolidations, in which the experience-dependent information redistributes over brain circuits.
- Consolidation is a dynamic, generative, transformative, and lingering process that is posited to balance maintenance of useful experience-dependent internal representations of the world with the need to adapt these representations to the changing world.
- The kinetics of consolidation appears to be a function of the dissonance between the novel information and the knowledge already available; experiences that fit available knowledge schemas may consolidate faster at the systems level and even skip the engagement of brain circuits that are essential for processing unexpected information.

agents" (Misanin et al., 1968). This reactivation-induced reopening of a consolidation-like window was termed "reconsolidation" (Nader et al., 2000; Sara, 2000; Dudai, 2004; Alberini, 2011). Reconsolidation does not seem to occur every time LTM is reactivated. It is more likely to occur when new information becomes available in the retrieval situation and when the reactivated representation is strong and controls behavior readily (reviewed in Dudai, 2004, 2012). These findings are in line with the hypothesis that in real life, reconsolidation may provide an opportunity for important memories to become updated.

The First Seconds of Systems Consolidation

How does consolidation start? Quite a lot is known on the processes that trigger synaptic consolidation and involve, as noted above, stimulus-induced modulation of gene expression (Kandel et al., 2014). However, insight into potential processes and mechanisms of the initiation of consolidation at the systems level is fragmentary. In a recent set of studies, Ben-Yakov and Dudai (2011) and Ben-Yakov et al. (2013, 2014) examined the first seconds following the inception of an episodic memory. They combined a protocol of "subsequent memory" with brief movie clips memoranda intercalated with brief rest periods. In subsequent memory type of protocols, activity of the subject's brain is recorded during encoding (usually using brain oxygenation-level-dependent [BOLD] signals in fMRI). The performance on a subsequent memory test is then correlated with the pattern of activation at encoding, leading to identification of brain activity signatures that predict the retrievability of subsequent memory. In the Ben-Yakov and Dudai (2011) paradigm, however, correlation was made not only with activity at the time of the on-line encoding of the prolonged naturalistic stimuli but also with the activity immediately after termination of these stimuli. This permitted tapping into memory-related processes during the first seconds after encoding.

A limited set of regions, consisting of the hippocampus, striatum, and cerebellum, demonstrated increased activity at the offset of the clips, with no apparent change in response during the events themselves. The activity in these regions was time-locked to the event offset and predictive of subsequent memory, and presentation of an immediate subsequent stimulus interfered with the memory of the previous stimulus and with the offset-locked hippocampal response, indicative of a potential role for this response in the "jump-starting" of consolidation. When using multiple repetitions to gradually increase clip familiarity, the hippocampal offset response was attenuated, in line with an encoding signal. Conversely, the onset response increased with familiarity, suggesting the online hippocampal response primarily reflects retrieval, rather than encoding (Ben-Yakov et al., 2014).

A large number of human neuroimaging studies find that the hippocampus is involved in the binding of separate episodic elements into cohesive units (e.g., Henke et al., 1997; Eichenbaum, 2004; Tubridy and Davachi, 2011). In rodents, at the offset of a learning trial, the hippocampus showed rapid forward and reverse replay of the firing sequence that occurred during the trial, and this was proposed to promote binding of episodic sequences (e.g., Foster and Wilson, 2006; Diba and Buzsáki, 2007; Carr et al., 2011; and see below). Understanding the relevance of the cellular data recorded in rodents to the human data requires human functional imaging methods with much higher resolution than fMRI. Nonetheless, even in the absence of human cellular data, the available fMRI results suggest that the offset-locked hippocampal response may underlie episodic binding, potentially triggered by the occurrence of an event boundary (Kurby and Zacks, 2008). Ben-Yakov et al. (2013) demonstrated that presentation of two distinct episodes in immediate succession elicited two distinct hippocampal responses, at the offset of each episode, consonant with the idea that the hippocampal response is shaped by the content of the stimulus and triggered by event boundaries.

As noted above, a hallmark of consolidation is the transient susceptibility of the memory to amnesic agents, including retroactively interfering stimuli (Wixted, 2004). When in their paradigm a clip event was immediately followed by an interfering stimulus, the offset response to the first clip was attenuated in a manner corresponding to the behavioral interference (Ben-Yakov et al., 2013). This is in line with the suggestion that the hippocampal offset-locked response constitutes a signature of, an early step in, the initiation of a consolidation process. The registration of episodes to long-term memory has been suggested to involve a hypothetical episodic buffer that can store episodes in working memory (Baddeley, 2000). While an episode is being experienced, its elements may automatically aggregate in such a buffer. The occurrence of an event boundary may then trigger the transfer of the contents of the postulated buffer to long-term memory, signaling the transition from encoding to the initial consolidation of the memory trace (Figure 1A). It is tempting to speculate that the hippocampal offset-locked response reflects this transition to consolidation.

The Minutes to Hours Thereafter

Investigation of systems consolidation, particularly in its first stages, classically focused on the hippocampal formation, which can be traced to the implication of hippocampal damage in

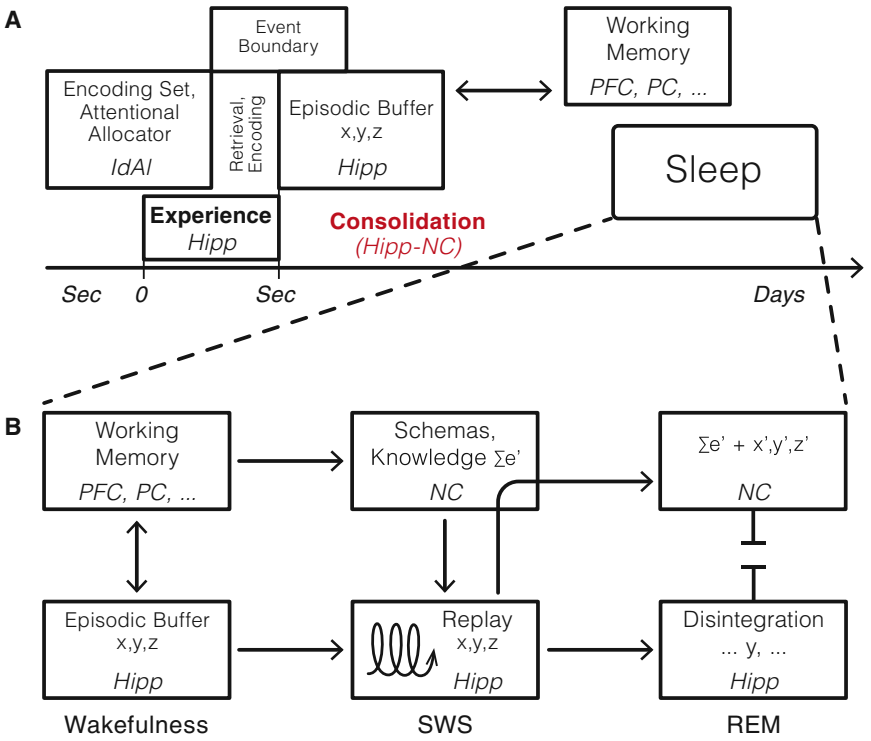

Figure 1. A Heuristic, Simplified Block Model of Selected Phases in Episodic Memory Consolidation

(A) The initiation of consolidation. Activation of a hypothetical encoding set precedes the event to be encoded, which is registered on the fly in the hippocampal system, involving rapid alternations of encoding mode (of the new information) and retrieval mode (of familiar attributes of the experience). An automatic episodic buffer, which also suberves working memory related to the ongoing task, is assumed to bind the incoming information into a coherent representation, the closure of which by a postulated event boundary sets into action the consolidation cascade.

(B) Consolidation during sleep. The episodic experiences (x,y,z) loading into the hippocampal-based buffer is accompanied by EEG theta activity and tagging of memories for reactivation during succeeding sleep. Reactivations that repeatedly occur during slow wave sleep stimulate the passage of the reactivated memory information toward neocortical storage sites where this memory information becomes integrated into pre-existing knowledge networks. Ensuing REM sleep stabilizes the newly formed neocortical representations via synaptic consolidation and might simultaneously degrade and disintegrate (large parts of) the hippocampal representation. For further details see text. *Hipp*, the hippocampal formation functioning in concert with parahippocampal cortici; *IdAI*, left dorsal anterior insula; *MTL*, mediotemporal lobe; *NC*, neocortex; PC, parietal cortex; *PFC*, prefrontal cortex, *SWS*, slow wave sleep. For further details see text.

amnesia (Scoville and Milner, 1957; Squire, 2004; Squire et al., 2001). However, ample evidence indicates that neocortical regions are also involved in the formation of memory already in its encoding phase (e.g., Paz et al., 2007; Barker and Warburton, 2008) or even in initiating an ''encoding set'' (i.e., the hypothetical state of readiness or predisposition to encode immediately prior to encoding; reviewed in Cohen et al., 2015) (Figure 1A). Studies in both animal models and humans demonstrate that within the first minutes to hours after encoding, distinct neocortical regions are engaged in processing that either predicts or is proven obligatory for subsequent memory. Tse et al. (2011) reported that in paired associate memory in the rat, learning of information that is postulated to be capable of being rapidly integrated into an existing knowledge schema, is associated with upregulation within minutes to hours of immediate early genes in the prelimbic region of the medial prefrontal cortex (mPFC), and pharmacological interventions targeted at that area can prevent both consolidation of new learning and the recall of recently and even remotely consolidated information. This finding was taken to support a model of consolidation that posits that systems consolidation could be accomplished quickly, even within hours, provided a previously established body of related knowledge, i.e., a mental schema, is available (Tse et al., 2007); this model will be further referred to below.

Guided by the same notion, that prior knowledge determines the kinetics of systems consolidation, van Kesteren et al. (2010) reported, using fMRI, that hippocampal-neocortical crosstalk in humans occurs during, and persists off-line, in the minutes after learning. Specifically, prior schema knowledge in a movie memory protocol was correlated with more vmPFC intersubject synchronization and less hippocampal-vmPFC connectivity during encoding, and this connectivity pattern persisted during a 15 min postencoding rest. The authors took these findings to suggest that additional crosstalk between hippocampus and vmPFC is required to compensate for difficulty integrating novel information during encoding and initiation of consolidation.

Memory-predictive functional connectivity between the hippocampus and neocortex in the first minutes after encoding in humans was also reported by Tambini et al. (2010). They examined if hippocampal-cortical BOLD signal correlations during rest periods following an associative encoding task are related to subsequent memory performance and reported enhanced functional connectivity between the hippocampus and a portion of the lateral occipital complex (LO) during rest following a task with high subsequent memory, but not during rest following a task with poor subsequent memory. Furthermore, the magnitude of hippocampal-LO correlations during the postencoding minutes predicted individual differences in later associative memory. All in all, the data from both animal models and human studies (see also Vilberg and Davachi, 2013) are consonant with the assumption that memory information becomes distributed across cortico-hippocampal circuits already at the early stages of consolidation.

It is of note that although the processes reported in the aforementioned studies are ascribed to a time window of minutes to hours after encoding, other protocols (e.g., see The First Seconds of Systems Consolidation) and particularly imaging methods with improved temporal resolution might unveil faster

kinetics of engagement of distinct brain areas as well as multiplicity of consolidation subprocesses. Furthermore, given, as noted above, that some neocortical areas were implicated already in encoding, further studies are required to determine which processes indeed involve offline reorganization of the circuits that encode the experience-dependent representational elements, i.e., the expected signature of systems consolidation. And last, but not least: that hypothetical processes of systems consolidation can be detected immediately after encoding, i.e., within the same time window as synaptic consolidation, is in line with the proposal that synaptic consolidation is a mechanistic subroutine of systems consolidation, and both are manifestations of the same memory transformation and stabilization process (Dudai, 2012).

The Hours to Days Thereafter

In real life, the period of hours to days after encoding is bound to involve sleep. In recent years, the understanding of the processes and mechanisms of consolidation in this time interval was advanced by studies of the role of sleep in memory (Diekelmann and Born, 2010). Of note, some of the post-encoding mechanisms discussed in the context of sleep, are also relevant to events that take place already minutes after encoding and discussed above; the time slices that we selected to describe in this Perspective do not imply that they are natural kinds, but rather, a convenient methodological taxonomy for the discussion of the ontogeny of a consolidated memory.

Numerous studies have demonstrated that a period of sleep in the hours after encoding prevents the rapid forgetting of the newly learnt materials (Rasch and Born, 2013). The prevailing explanation of sleep's benefit for memory was that sleep protects the newly encoded and still labile trace from retroactive interference, assuming that during sleep the brain would not encode new information that may overwrite the learnt materials. The notion of sleep as a brain state actively promoting systems consolidation became a focus of research only recently, based on studies demonstrating the reactivation of spatial representations in the same hippocampal networks that were activated during a training session before sleep (Pavlides and Winson, 1989; Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996). The replay of firing patterns observed in place cell assemblies of rats during sleep is in the same sequence as during prior training, but progresses at a faster speed (O'Neill et al., 2010). It is a robust phenomenon within the first 30 min of sleep after training. Notably, such neural reactivations are seen during slow-wave sleep (SWS), but very rarely during rapid eye-movement (REM) sleep (e.g., Kudrimoti et al., 1999; Poe et al., 2000), i.e., the sleep stage traditionally linked with dreams and the re-processing of memory. Neuronal reactivation is not restricted to the hippocampus, but spreads to extra-hippocampal regions and has been identified in the striatum and neocortical areas (Lansink et al., 2008; Euston et al., 2007). In the hippocampus, neuronal replay occurs during sharp wave-ripples, the ripples representing local field potential oscillations ~180 Hz (in rats) (Diba and Buzsáki, 2007). The experimental induction of neural reactivation by cuing the newly encoded memory during SWS with associated olfactory and auditory stimuli was reported to enhance the cued memory (Rasch et al., 2007; Oudiette and Paller, 2013; Hu et al., 2015). This indicates an instrumental role of reactivation during sleep in memory consolidation. Still, it is unclear what drives the reactivation of a specific memory representations during sleep in natural conditions. Sleep seems to only enhance select memories. EEG theta coherence in a network integrating hippocampus with frontal cortical circuitry and other structures has been suggested as a mechanism that tags specific representations at encoding for sleep-associated reactivation and consolidation (Benchenane et al., 2010; Inostroza and Born, 2013). The molecular mechanisms of this tagging are possibly unique to sleep-dependent consolidation and may differ from those synaptic tag-and-capture mechanisms (Frey and Morris, 1997; Martin et al., 1997) that have been hypothesized to underlie retroactive enhancement of weakly encoded associative memories by subsequent salient stimuli during wakefulness (Redondo and Morris, 2011; Dunsmoor et al., 2015).

Like the aforementioned consolidation processes in the first minutes after encoding, neural memory reactivations during SWS do not occur in isolation but are rather embedded in a dialog between hippocampus and neocortex (Buzsáki, 1989; Diekelmann and Born, 2010). This interregional communication was reported in studies of local field potential oscillations that revealed a phase nesting of the three major types of local field potent oscillations during SWS: the <1 Hz slow oscillations that originate from neocortex, the 12–15 Hz spindles that originate from thalamus and spread to cortical and hippocampal networks, and the ripples that accompany neural reactivations in hippocampal networks. It was proposed that the neocortical slow oscillation through its depolarizing up-state drives, via descending pathways, the generation of thalamic spindles and hippocampal ripples, thereby allowing for the formation of "spindle-ripple events," where ripples and associated reactivated memory information become nested into the successive excitable phases of the spindle oscillation (Sirota et al., 2003; Clemens et al., 2007). Spindle-ripple events are thought of as a mechanism that supports the hippocampus-to-neocortical passage of the reactivated neuronal information, in which this information reaches the neocortex still during the excitable up-state of the slow oscillation. Spindles appear to be most closely linked to the sleep-induced improvement in memory and cortical integration of new information into preexisting knowledge networks (Fogel and Smith, 2011; Studte et al., 2015; Tamminen et al., 2010; Friedrich et al., 2015). They are also associated with processes of synaptic plasticity that might enable the underlying redistribution of elements of the neuronal representations to neocortical and other extrahippocampal sites (Rosanova and Ulrich, 2005; Bergmann et al., 2012; Aton et al., 2014; Blanco et al., 2015). In theory, any redistribution at the circuit level could be assumed to result in transformation of the representational, hence mnemonic, content.

Studies using fMRI in humans corroborated the notion of sleep supporting the redistribution of elements of declarative memory representations toward extra-hippocampal, predominantly neocortical sites (Takashima et al., 2006; Gais et al., 2007). There is also growing evidence that this sleep-associated redistribution of information is accompanied with an increased semantization of memories and the abstraction of gist information from episodic representations (e.g., Payne et al., 2009; Wilhelm et al.,

2013; Friedrich et al., 2015; also see on later stages of consolidation below).

In the following, we discuss three issues of controversy concerning consolidation and sleep.

The Role of REM Sleep

While early phases of systems consolidation appear to happen mainly during non-REM sleep and specifically during SWS, the contribution of REM sleep to this process is still unclear. Based on the fact that REM sleep always follows SWS, the so-called "sequential hypothesis" assumes that REM sleep completes a certain process induced during prior SWS. Specifically, it has been proposed that spindle activity during SWS leads to massive local Ca^{2+} influx into neurons and thus stimulates the induction of calcium-dependent plasticity factors like the immediate early genes Zif-268 (Egr1) and Arc during the ensuing REM sleep (Ribeiro et al., 2007; Ribeiro, 2012). This view that REM sleep is acting to complete SWS-induced systems consolidation by promoting synaptic consolidation processes, is however challenged by evidence indicating that the cascade of molecular processes underlying synaptic potentiation and even sprouting of synaptic boutons can also be induced during sleep periods in the absence, or with only negligible amounts, of REM sleep (Chauvette et al., 2012; Yang et al., 2014). Behavioral studies likewise provide a mixed picture. REM sleep seems to benefit particularly memory that is not dependent on cortico-hippocampal circuitry, including procedural skills, object recognition memory, and amygdala-mediated cued fear conditioning (Karni et al., 1994; Plihal and Born, 1997; McDevitt et al., 2014; Popa et al., 2010; also see below), as well as stimuli conforming with preexisting schemas (Durrant et al., 2015). These observations could indeed be parsimoniously explained by assuming a stabilization effect mediated via local, synaptic consolidation. Furthermore, REM sleep in certain skill tasks seems to add a critical factor for synaptic consolidation that is otherwise afforded by a sufficiently long interval of wakefulness (Karni and Sagi, 1993; Karni et al., 1994; Karni, 1995). However, others have suggested that beyond stabilizing memory, REM sleep contributes to the reorganization of representations during system consolidation, e.g., by loosening the bonds of associative memory representations and thereby disintegrating elements of these memories (Stickgold and Walker, 2013; Korman et al., 2005; Cai et al., 2009; Sterpenich et al., 2014; Landmann et al., 2015). Still, such disintegrating role of REM sleep in consolidation might stem from random activation of neural networks or from a non-discriminatory degrading influence on hippocampal representations associated with REM sleep theta activity (Grosmark et al., 2012), rather than from specific memory reactivation as observed during SWS (Figure 1B).

Reactivation during Sleep versus Wakefulness

Replay of firing patterns in hippocampal neuron assemblies also occurs during quiet wakefulness and in the short breaks a rat takes while performing on a maze task (Diba and Buzsáki, 2007). Different from reactivations during SWS, wake reactivations can take place in both forward and backward replay direction. The existence of wakefulness replay has been taken to question the unique role of sleep in systems consolidation and to argue that consolidation proceeds during quiet wakefulness in basically the same way as during sleep. However, SWS and wakefulness are two brain states with partly opposing neurochemical and electrophysiological features (see below). Therefore, it seems counterintuitive that neural assembly reactivations occurring in these states should produce the same result. It has been proposed that conditions during wakefulness favor the uptake of information into neocortical and hippocampal networks, whereas SWS favors the flow of information back from hippocampus toward entorhinal and neocortex (Buzsáki, 1989; Hasselmo and McGaughy, 2004; Rasch et al., 2006). This proposed division of labor may, however, oversimplify the situation in situ (Wagner et al., 2010).

Acetylcholine has been identified as one of the key determinants of information processing and flow in and out of the hippocampus. Cholinergic activity is high during wakefulness and in this state suppresses, via intrahippocampal recurrent presynaptic inhibition, output to extrahippocampal target regions (Hasselmo and McGaughy, 2004). SWS is characterized by reduced cholinergic activity and, consequently, by the release of CA1 output from this inhibition. Glucocorticoid signaling probably adds to this shifting of network activity between a wakefulness mode of encoding and a SWS mode of consolidation, because their release is naturally suppressed to minimum levels during nocturnal SWS (Wagner and Born, 2008; Kelemen et al., 2014; Payne and Nadel, 2004).

It is also still unclear whether reactivations during SWS labilize memory in the same way as reactivations during waking. Diekelmann et al. (2011) used odors associated with learned visuospatial memories (involving card locations) for cuing and hence reactivating these memories during post-learning periods of wakefulness or of sleep (containing no REM sleep). They found that only after wake reactivation, the memories were susceptible to the impairing influence of interference learning. Odor-induced reactivation during SWS produced immediate strengthening of the memory, apparently overleaping a period of labilization that has been deemed critical to the reorganization of memory representations during systems consolidation. Contrary to these findings in humans, a study in mice suggests that reactivation during SWS labilizes the memory similarly to reactivation in wakefulness (Rolls et al., 2013), although perhaps more transiently. The study used a classical fear conditioning paradigm, where foot shock was paired with an odor. Re-exposure to the odor during SWS after conditioning enhanced the conditioned fear response. However, when the mice were bilaterally injected with a protein synthesis inhibitor (i.e., an amnesic agent) into the amygdala prior to sleep, reactivations during SWS diminished the conditioned fear response. It is noteworthy that the latter finding indicates that the postulated reactivation-induced reconsolidation during sleep, like the postulated reconsolidation of memories during wakefulness, involves new protein synthesis. Nonetheless, it is still unknown to what extent reconsolidation processes induced during wakefulness and sleep differ in their molecular underpinnings (e.g., Lee et al., 2004; Ribeiro, 2012).

Systems Consolidation during Sleep: Unsupervised Learning?

Another open issue is what guides consolidation during sleep (Box 2). Do the consequences of neural reactivation during sleep

Box 2. Future Directions

- Is consolidation a natural kind of neuronal and brain process that reflects a dedicated phase in establishing memory storage, or is it a term and a concept that conceal a very wide spectrum of memory-related plastic and transformative processes and whose usefulness in triggering and promoting new models and research projects should be reassessed?
- What are the specific roles of synaptic changes, cell-wide changes, and nuclear changes, all of which are detected in the course of consolidation processes, in storing versus accessing and expressing items in long-term memory over months and years?
- What are the brain mechanisms that initiate, drive, direct, and constrain the redistribution of elements of memory representations over brain circuits during systems consolidation, and does the process ever end?
- Is systems consolidation unique to memory circuits that involve the hippocampus? Systems consolidation has been found to impact representations of skill memories as well, yet it is still unclear whether this occurs in real-life in non-amnesic individuals independently of any engagement of the hippocampal system.
- To what extent is sleep critical to systems consolidation? Does it merely optimize a process that is otherwise established in the same way during wakefulness? Alternatively, consolidation during sleep might differ in quality from that in the waking brain, e.g., sleep might provide unique conditions of unsupervised learning where memory reactivations allow for an unbiased abstraction and integration of gist information into long-term knowledge networks.

depend on evaluative feedback originating from comparison processes in memory, or from brain circuits signaling aversiveness and reward? With respect to reactivation of memory during wakefulness, it has been argued that the induced cycle of labilization and reconsolidation enables the updating of items in memory (Forcato et al., 2014; Hupbach et al., 2008; Rasch and Born, 2007). Thus, reactivating cues producing stronger mismatch may be more effective in labilizing a memory representation (Osan et al., 2011). Yet, during sleep there is naturally no external stimulus input that could be used for meaningfully updating a representation. Hence, one may hypothesize that, instead of external cues, reactivated pre-existing schemas in neocortical sites direct sleep-dependent consolidation, for example, by favoring the hippocampal reactivation of that memory information that fits the pre-existing schema. Schema-guided consolidation has been revealed during wakefulness (see above) but evidence for a similar action of schemas on sleep-dependent consolidation is lacking (Inostroza and Born, 2013; Durrant et al., 2015).

As to the potential role of reward circuits in driving consolidation in sleep, recent findings suggest that the concurrent (re-) activation of dopaminergic reward circuitry can enhance the strengthening effect of memory reactivation during SWS (de Lavilléon et al., 2015; Feld et al., 2014). Also, reactivating conditioned fear memories during SWS in humans by presenting the conditioned stimulus alone, in the absence of the aversive unconditioned stimulus, induced an extinction-like effect (He et al., 2015; Hauner et al., 2013). However, two rodent studies that cued fear memories during SWS by repeatedly presenting the conditioned stimulus, found the opposite, i.e., strengthening of the originally learnt fear memory (Rolls et al., 2013; Barnes and Wilson, 2014). All in all, whether memory consolidation during sleep represents unsupervised learning (Margoliash and Schmidt, 2010) or a process whose efficacy critically depends on evaluative feedback mechanism, remains an open question.

The Months and Years Thereafter

In line with the early clinical observations that have contributed to the emergence of the consolidation hypothesis in the first place (Ribot, 1977; Burnham, 1903), a number of studies of "global" amnesics, damaged in the medial temporal lobe (MTL), reported temporally graded retrograde amnesia on tasks that presumably engage declarative memory, spanning months to years. Some studies using animal models of amnesia also reported that the hippocampus is required for LTM for only a limited time after encoding (Squire et al., 2001). Later studies, however, reported the absence of such amnesic gradient (Sutherland et al., 2008; Sutherland and Lehmann, 2011; Broadbent and Clark, 2013) or mixed results depending on the protocol (Winocur et al., 2013). In addition, some functional brain imaging studies in healthy human participants reported reduced recollection-correlated activity in mediotemporal structures but increased neocortical activity over time (e.g., Smith and Squire, 2009; see also in Smith et al., 2010). Similar conclusions were proposed on the basis of metabolic mapping in laboratory animals (Bontempi et al., 1999; Frankland et al., 2004; Ross and Eichenbaum, 2006; Wheeler et al., 2013).

A dominant model intended to account for those data that indicated slow progressing graded retrograde amnesia is the "standard consolidation theory" (McClelland et al., 1995; Squire, 2004). This model posits that the hippocampus is only a temporary repository for memory whereas the neocortex stores the memory thereafter. Specifically, the model postulates that encoding, storage, and retrieval of declarative information is initially dependent on both the hippocampal complex and on the neocortical areas relevant to the encoded stimuli. The hippocampal trace is probably a compressed version of the representation. Over time, the information reorganizes, by recurrent replay of the hippocampal representation to the neocortex (that is initiated already shortly after encoding, see above). This reinstates the corresponding neocortical memory, resulting in incremental adjustments over time of neocortical connections and establishment of a long-lasting, reorganized representation, while the hippocampal representations decay.

Over the years, however, some evidence has accumulated that seems incompatible at least with some aspects of the standard consolidation theory. First and foremost, the effect of MTL lesions on sub-types of human declarative memory was reported not to be the same, with autobiographical episodes being most severely affected. The retrograde temporal gradient for this type of memory is either entirely absent or very shallow, sparing only memories acquired several decades earlier. Driven by these observations and complementary findings in animal models of

amnesia (and see also above on more recent conflicting reports in animal models), Nadel and Moscovitch (1997) proposed an alternative, the "multiple trace theory." This model posits that the hippocampal formation rapidly and obligatorily encodes all episodic information. The episodic information, sparsely encoded in distributed ensembles of hippocampal neurons, acts as an index for neocortical neurons that attend the information and binds them into a coherent representation. The resulting hippocampal-neocortical ensemble constitutes the memory trace for the episode. Since reactivation of the trace commonly occurs in an altered context, it results in newly encoded hippocampal traces, which in turn drive new traces in the neocortex. This results in multiple traces that share information about the initial episode. Over time, so goes the model, 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 continues, however, to depend on the hippocampus as long as the memory exists. An update of the "multiple trace theory," the "trace transformation theory," emphasizes abstraction and transformation of hippocampus-neocortical episodic information into neocortical semantic representations (Winocur et al., 2010; Winocur and Moscovitch, 2011). The resulting gist memories are posited to co-exist and interact with those representations in which the context/episodicity is retained and that remain hippocampal-dependent.

In an attempt to tap into potential transformations over time of the episodic engram and its dependence on specific brain substrates, Furman et al. (2012) took fMRI snapshots of human brain activity over several months during retrieval of movie episodes. Three groups of participants watched a narrative movie and were then scanned during a memory test that taxed recognition, recall, and metamemory 3 hr, or 3 weeks, or 3 months later. Judging by performance, the richness and complexity of memory declined over time. High recognition accuracy after hours decreased after weeks but remained at similar levels after months. In contrast to this similar level of behavioral performance, BOLD activity in retrieval-related brain regions was positively correlated with recognition accuracy only after months. Hippocampal engagement during retrieval remained similar over time during recall but decreased in recognition. These results are consonant with two hypotheses: (1) that the episodic memory trace becomes transformed over time to a leaner form that is capable of supporting accurate retrieval of the crux of events with only minimal network activation, and (2) that the hippocampus subserves retrieval of real-life episodic memory long after encoding, its engagement being dependent on the retrieval demands. Both hypotheses are in line with the aforementioned "trace transformation theory," although of course do not prove that theory. Furman et al. (2012) further suggest that attainment of parsimonious, energy sparing brain activation, while still being able to recognize what did or did not happen, might have been the outcome of a selective pressure that had contributed to the evolution of systems consolidation.

In other sets of studies, the possibility was raised that the slow time course of systems consolidation is not a rigid given, but rather depends on the relevance of the new information to available knowledge (schema assimilation model) (Wang and Morris, 2010). Hence, so goes the proposal, systems consolidation could be accomplished quickly, within days or even hours, provided a previously established body of related knowledge, i.e., a mental schema, is available. This was illustrated by Tse et al. (2007), who trained rats on hippocampal-dependent flavor-location associations. After learning a set of different associations over a few weeks, a single trial learning was sufficient to rapidly consolidate the memory of a new association: while hippocampal lesion 3 hr after training disrupted subsequent LTM, a similar lesion at 48 hr was already ineffective, demonstrating that LTM for the new association 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 schema is a pre-requisite for rapid systems consolidation. The rapid schema-dependent learning was associated with upregulation of immediate-early genes in the medial prefrontal cortex, commonly indicative of ongoing cellular consolidation processes (Tse et al., 2011; and see above). The recently reported preferential consolidation of schema conformant information during sleep in humans, noted above (Durrant et al., 2015), is also in line with the schema assimilation model of systems consolidation.

It is of note that schema assimilation model resonates with the broader possibility that systems consolidation in some tasks and conditions that may be considered declarative can bypass the hippocampus very quickly or even from the outset. For example, complex associative processes that are deemed "declarative" and take place in early infancy are performed in spite of not yet having an integrated functional hippocampus (Mullally and Maguire, 2014). A potential example is "Fast Mapping," the process that permits toddler's rapid acquisition of words following a single exposure (Carey and Bartlet, 1978). A version of the Fast Mapping task was reported to involve in adults rapid neocortical acquisition potentially independent of the hippocampus (Sharon et al., 2011; see also Merhav et al., 2014, 2015; but see Smith et al., 2014, for reservations concerning explicitness and consolidation into long-term memory independent of hippocampus).

Consolidation and Transformation in "Non-declarative" Memory

Whereas synaptic consolidation is considered universal, hence, irrespective of the memory system engaged (Dudai, 2012; Kandel et al., 2014), the hypothetical process of systems consolidation is most commonly discussed within the context of declarative memory and its dependence on cortico-hippocampal circuitry. Even the aforementioned reports that prior knowledge schemata shape the engagement of the hippocampus in declarative consolidation, are anchored in the conceptual framework that the cortico-hippocampal system is the default hub of novel declarative information. But is systems consolidation unique to cortico-hippocampal circuits? If evolution is a clue, then the answer tends toward the negative side, since there are indications that systems consolidation, including its sleep-dependency, represents an evolutionary preserved mechanism of memory formation that occurs in birds and bees, in structures not homologous to the mammalian hippocampus (Vorster and Born, 2015). But once the hippocampal system made its appearance, did it become a must for consolidation?

This question is linked to a different one, i.e., whether tasks classically considered as generating "non-declarative" memory and in amnesic individuals are independent of "declarative" memory circuits, are also performed independently of the hippocampal system in non-amnesic individuals in real life situations. An alternative, more realistic possibility is that both "declarative" and "non-declarative" circuits and computations function in concert (Henke, 2010; Cabeza and Moscovitch, 2013). For example, in skill learning, a training experience will often result in some trace of declarative memory at the minimum, and healthy participants will be able to recall that they took part in the training session and often recall some aspects of the task. Neuroimaging studies show that the hippocampus is engaged during training experience that can lead to skill. Furthermore, the level of hippocampal engagement and its subsequent disengagement may determine whether an individual will be a good learner and how well skill will be consolidated (Albouy et al., 2015). Thus, there is evidence that cortico-striatal and hippocampal-dependent memory systems do not act independently, but rather interact during consolidation (Debas et al., 2014; Coynel et al., 2010; Albouy et al., 2015). The reverse also holds true: brain circuits that are traditionally associated with non-declarative tasks participate and predict subsequent memory in declarative tasks (Ben-Yakov and Dudai 2011; Reber et al., 2012). The caveat concerning the distinction between "declarative" and "non-declarative" memory systems in non-amnesic individuals notwithstanding, evidence exists to suggest that systems consolidation, i.e., circuit-level redistribution of experience-dependent representational information over time, can occur in tasks that can be acquired independently of the hippocampus and MTL.

The initial evidence for memory consolidation induced by protocols of skill acquisition in humans came from perceptual and motor skill learning paradigms (Karni and Sagi, 1993; Karni et al., 1994, 1995, 1998; Brashers-Krug et al., 1996). Indeed, it was in the context of such studies that the notion was established of sleep being effective and in some tasks critical for the completion of consolidation (Karni et al., 1994; Karni, 1995; Korman et al., 2007). However, an indispensable role of sleep in consolidation in all skill learning conditions and age groups was questioned (Karni et al., 1994; Karni, 1995; Roth et al., 2005; Ashtamker and Karni, 2013). Thus, while sleep is generally beneficial in consolidating skill, it might be critical only in a select kind of tasks, particularly in those requiring movement sequence learning, generating new movement routines (Korman et al., 2007; Debas et al., 2010, 2014). However, during the acquisition phase, these are the tasks that seem also to particularly profit from an engagement of hippocampal circuits in healthy adults (Henke 2010). Given that sleep preferentially benefits memories encoded via hippocampal-prefrontal cortical circuitry (see above), it has been proposed that distinct aspects of the movement sequence learning experience are sleep-dependent because of the involvement of the hippocampal system in the acquisition (Albouy et al., 2013a, 2013b; Inostroza et al., 2013; Inostroza and Born, 2013). Nevertheless, the proposal that the sleep dependency of consolidation process induced in skill acquisition can be attributed mainly to the hippocampal system remains undecided. Notably, the sleep process most closely linked to skill consolidation appears to be spindles occurring during SWS and non-REM sleep stage 2 (Fogel and Smith, 2011; Spoormaker et al., 2011; Barakat et al., 2011, 2013; Debas et al., 2010, 2014; Ackermann and Rasch, 2014; Wilhelm et al., 2012), although these may differ from the ones directly implicated in hippocampus-dependent consolidation.

Systems level changes can express themselves in behavior as qualitative change in performance, indicating that a different task solution is implemented as experience accumulates after the hypothetical consolidation phase (Korman et al., 2003; Sosnik et al., 2004, 2014; Boutin et al., 2012; Krakauer and Shadmehr, 2006; Stickgold and Walker, 2013). The proposal is that during consolidation, new representational elements with different tuning properties are recruited for skill performance and become dominant after the consolidation phase. First, performance at a novice level is qualitatively different from performance after extensive practice; for example, new, specific task solution routines and novel abilities and movement elements emerge in between the training sessions (e.g., Sosnik et al., 2004, 2014; Korman et al., 2003; Rozanov et al., 2010). Second, inferred system level changes are also reflected in changes in the ability to transfer gains across shifting stimuli, contexts, and task parameters, in different phases of experience (e.g., Karni and Sagi, 1993; Korman et al., 2003; Karni and Korman, 2011; Censor, 2013). Again, the proposal is that the ability to transfer the gains accrued in training changes because different representations, even within a given processing stream, are tuned to different aspects of the experience, with some new aspects being established in-between sessions, during the hypothetical consolidation phase (Karni and Korman, 2011). For example, the ability to transfer an acquired motor skill from a trained to an untrained hand suggests that the performance routine is based on units that represent movement irrespective of the motor effector. However, a growing inability to transfer skill across hands, when additional training sessions are afforded, suggests that the performance routine has been redistributed or even migrated to units or areas that represent movement of only one (the trained) effector but not the other (e.g., Korman et al., 2003; Rozanov et al., 2010; Censor, 2013).

Studies in the monkey (Hikosaka et al., 1999, 2002) and functional neuroimaging in humans (Doyon and Benali, 2005) suggest that as experience in skill performance accumulates, new brain networks become dominant for performance by taking over the mnemonic representation of the task (for review see Krakauer and Shadmehr, 2006; Ungerleider et al., 2002). More recent imaging studies support the notion that in the post training-session interval (including sleep), brain activity shifts and undergoes significant changes in cortical-subcortical networks other than the hippocampal system (e.g., Debas et al., 2014; for a review see Dayan and Cohen, 2011). These changes occurred in multiple brain areas, reflected in changes in activity and in connectivity patterns in the brain networks underlying task performance at a later re-test. One important focus of interest are the changes occurring during consolidation in cortico-striatal networks, specifically redistribution of new experience-dependent information between sub-networks (Lehéricy et al., 2005; Albouy et al., 2015). A second focus is the motor cortex itself.

Rodent models and the application of in vivo two-photon microscopy to image dendritic spine dynamics (Xu et al., 2009; Yang et al., 2009; reviewed in Yu and Zuo, 2011) show that at

the cellular level, training leads to rapid formation of enduring postsynaptic dendritic spines on the output pyramidal neurons in the contralateral M1 (primary motor cortex). Furthermore, a role for sleep, specifically SWS, was suggested in the selective maintenance and promotion of the dendritic spines relevant to task performance (Yang et al., 2014). Recent fMRI experiments suggest the possibility of a selective effect of an overnight consolidation interval in young human adults at the systems level as well (Gabitov et al., 2014, 2015). Notably, the execution of a consolidated finger opposition sequence was characterized by a distinct dynamic pattern (repetition enhancement) in the contralateral M1 and, bilaterally in the medial-temporal lobes. Other systems change occur as well. Connectivity analyses suggest that a network including M1 and striatum underlies online motor working memory that is postulated to promote a transient integrated representation of an unfamiliar movement sequence. It is suggested that this working memory network becomes unnecessary when a consolidated movement sequence representation is retrieved from M1 following the systems level redistribution of information that presumably occurs overnight.

Taken together, the human and mice data suggest that task-specific durable motor memories can be established during a rather brief (hours, including sleep) consolidation period in motor cortex. In line with the idea that synaptic consolidation is a subroutine of systems consolidation (see above), these traces may be further shaped and strengthened as experience accumulates through recurring post-training cycles of synaptic plasticity that promote and establish connectivity changes in brain network in which the motor cortex serves as hub. The motor skill memory data can be interpreted as suggesting that the local representation of a trained movement sequence is enhanced during offline periods in-between training sessions by the incorporation of new units into the local network sustaining the memory trace (e.g., Nudo et al., 1996). This expanded representation can shift the balance of the local network to a different output, culminating in a shift in the memory hub.

Consolidation and Transformation: Concepts, Terms, and Natural Kinds

The concept of consolidation emerged, at first implicitly (Quintilian, *Inst. Orat.* 11.2.43, trans. Butler, 1921) and later explicitly (Muller and Pilzecker, 1900), in an attempt to account for the experimental evidence that items in memory change their susceptibility to forgetfulness or interference over time. This has led to impressive research programs that considered consolidation as a biological reality and attempted to decipher its mechanistic underpinnings (McGaugh, 2000; Kandel et al., 2014). In the process, the concept of consolidation was translated into the idea that it is a well-defined time-limited mechanism to "fixate" memories (Glickman, 1961; McGaugh, 1966).

Naturally, as research advanced, so did the interpretation of the concept. The "fixation" idea was mostly abandoned, particularly with the reemergence of the "reconsolidation" hypothesis (Nader et al., 2000; Sara, 2000; Dudai, 2004). Furthermore, the notion was revitalized that consolidation is also a generative process, resulting in modification and reconstruction of experience-dependent internal representations (Bartlett, 1932; Dudai, 2004, 2012; Schacter and Addis, 2007; Karni and Korman, 2011; Winocur and Moscovitch, 2011). At the same time, one should not overlook the postulated role of consolidation in balancing stability and change and maintaining adaptive predictive power of representations. How this is achieved is a key question that hovers over consolidation research at multiple levels of analysis. Just as an example, the possibility should not be excluded that major steps in systems consolidation take place during sleep because this allows transient offline stability of representations on the one hand, yet, on the other hand, permits generative manipulation of representations in the absence of the need to test their adaptability on the fly in real space while they undergo permutational reconstruction in offline mental space.

The question also arises, however, whether consolidation is at all a natural kind (Quine, 1970), or merely a heuristic umbrella term for a rather wide spectrum of brain mechanisms that maintain and transform internal representations over time to adapt them to a changing environment. Appreciation of the artificiality of a term is not merely a semantic issue. It promotes fine dissection of processes and mechanisms, reduces the risk of paradigmatic stagnation, and paves the way to new findings, models, and interpretations. The mere existence of synaptic/cellular consolidation is not contentious (Dudai, 2012; Kandel et al., 2014). It is the systems level of the concept that is still rather plastic. The current view of systems consolidation tilts toward considering it as a family of transformative processes that keep the memory trace restless rather than stable and that linger for long, perhaps even for as long as the memory is viable. Ongoing instability may fit declarative information more than skill, but as noted above, the rigid distinction between declarative and non-declarative memory systems seems also to fade away. In studying consolidation, we should therefore expect to uncover, instead of a monolithic type of biological mechanism, sets of mechanisms at multiple spatiotemporal scales, that generate the aforementioned balance of stability and instability that may possibly benefit a specific type or token of the representation studied. The term consolidation (from Latin "make firm together") is well-rooted in the memory literature and therefore deserved not to be reconsolidated even in systems level discussion, but recent research, part of which is briefly reviewed above, indicates that in the memory dictionary, its translation is ongoing transformation, not fixation.

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