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The Consolidation and Transformation of Memory

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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