

Cellular and systems consolidation of declarative memory

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Abstract

For memories to last consolidation has to occur, with this chapter referring to both cellular consolidation and systems consolidation. Cellular consolidation takes place in the hours after learning, stabilizing the memory trace – a process that likely involves structural changes in hippocampal neurons. Systems consolidation refers to a more protracted process by which memories eventually become independent of the hippocampus as they are established in cortical neurons. Both forms of consolidation may serve to render memories less vulnerable to forgetting. Although generally treated separately, these two forms of consolidation are presumably closely related. In this chapter, we will provide an overview of both cellular and systems consolidation and how they interact. Further, we will discuss effects of novelty, sleep and previous knowledge on consolidation.

Introduction

The modern idea that memories require time to consolidate has a long history. In 1900, the German experimental psychologists Georg Müller and Alfons Pilzecker published a monograph in which they proposed a new theory of memory and forgetting, one that included – for the first time – a role for consolidation. According to Müller and Pilzecker's (1900) view, consolidation consists of a physiological process that perseverates and eventually renders the memory trace less vulnerable to interference caused by new learning (Wixted and Cai 2013).

Although Müller and Pilzecker (1900) are credited with conceiving of the concept, the main impetus for the study of consolidation can be traced to Patient HM. Following bilateral medial temporal lobe resection to control his epileptic seizures, HM was unexpectedly left with a profound case of anterograde amnesia (i.e., the inability to form new memories from that point on) despite retaining normal perceptual and intellectual functioning, including normal working memory capacity (Scoville and Milner 1957). Critically, HM also exhibited temporally graded retrograde amnesia (Squire 2009). That is, memories that were formed prior to surgery were also impaired, and the degree of impairment was greater for memories that had been formed just prior to surgery than for memories that had been formed well before. Although memories of up to 3 years prior to his surgery appeared to be somewhat impaired, HM's older memories were apparently intact (Scoville and Milner 1957). This result suggested that medial temporal lobe structures are involved in the maintenance of memories for a limited period of time after the memory is formed. In other words, memories consolidate in that sense as well.

Memory consolidation is now a multifaceted concept. At a minimum, it refers to both cellular consolidation and systems consolidation. Cellular consolidation takes place in the hours after learning, stabilizing the memory trace – a process that likely involves structural changes in hippocampal neurons. Systems consolidation refers to a more protracted process by which

memories eventually become independent of the hippocampus as they are established in cortical neurons. Both forms of consolidation may serve to render memories less vulnerable to forgetting. Although generally treated separately, these two forms of consolidation are presumably closely related and are perhaps best conceptualized as different stages of the consolidation process that Müller and Pilzecker (1900) conceived of more than a century ago.

Cellular Consolidation

Hebb postulated that when two neurons repeatedly fire together, they become more likely to fire together again in the future. The mechanism underlying this durable change in the coordinated firing propensities of two neurons is termed cellular consolidation. Investigations into the mechanisms of cellular consolidation have used a wide array of model systems, ranging from *Aplysia* to the mammalian hippocampus. Since the early 1970s, these investigations have led to a series of insights, beginning with the seminal discovery of long-term-potential (LTP, (Bliss and Lomo 1973)) and continuing with our still growing understanding of the role of CREB and plasticity-related immediate early gene expression (Bailey et al. 2015).

LTP refers to a long-lasting increase in synaptic strength following high-frequency stimulation of the pre-synaptic neuron. While there are many types of LTP (for review see (Bailey et al. 2015)), the classic form is NMDA receptor dependent LTP: in response to high-frequency stimulation, the excitatory neurotransmitter glutamate is released from the presynaptic neuron and binds to post-synaptic AMPA receptors, depolarizing the post-synaptic neuron (causing it to fire) and opening a channel in the post-synaptic NMDA receptors. The open NMDA channel results in an influx of calcium ions into the post-synaptic neuron, which, in turn, induces a molecular cascade of phosphorylation (Figure 1). Autonomously phosphorylated (and thus active) CaMKII and PKC phosphorylate existing AMPA receptors, increasing the conductance of the receptors already in the synapse, and triggering the insertion of additional AMPA receptors into synapse. These events are not dependent on protein synthesis and result in early-LTP, which refers to an increase in synaptic strength that will degrade in minutes (or a few hours at most) if not stabilized to late-LTP. Unlike early-LTP, which is independent of protein synthesis, late-LTP requires gene transcription and protein synthesis in the postsynaptic cell. The processes that lead to late-LTP will only occur if the tetanic stimulation of the pre-synaptic neuron is sufficiently strong. Many cytoplasmic and nuclear molecules are needed to ultimately result in the protein synthesis and morphological changes observed in late-LTP. Most significant among these is the transcription factor CREB, discovered by Eric Kandel. Together, these cascades lead to the stabilization of the new AMPA receptors in the cell membrane so that long-lasting synaptic potentiation is achieved. The importance of NMDA-receptor dependent LTP for memory was shown in a seminal study by Richard Morris, in which the inhibition of NMDA-receptors in the hippocampus prevented the induction of LTP and led to a memory deficit in the spatial watermaze task (Morris et al. 1982).

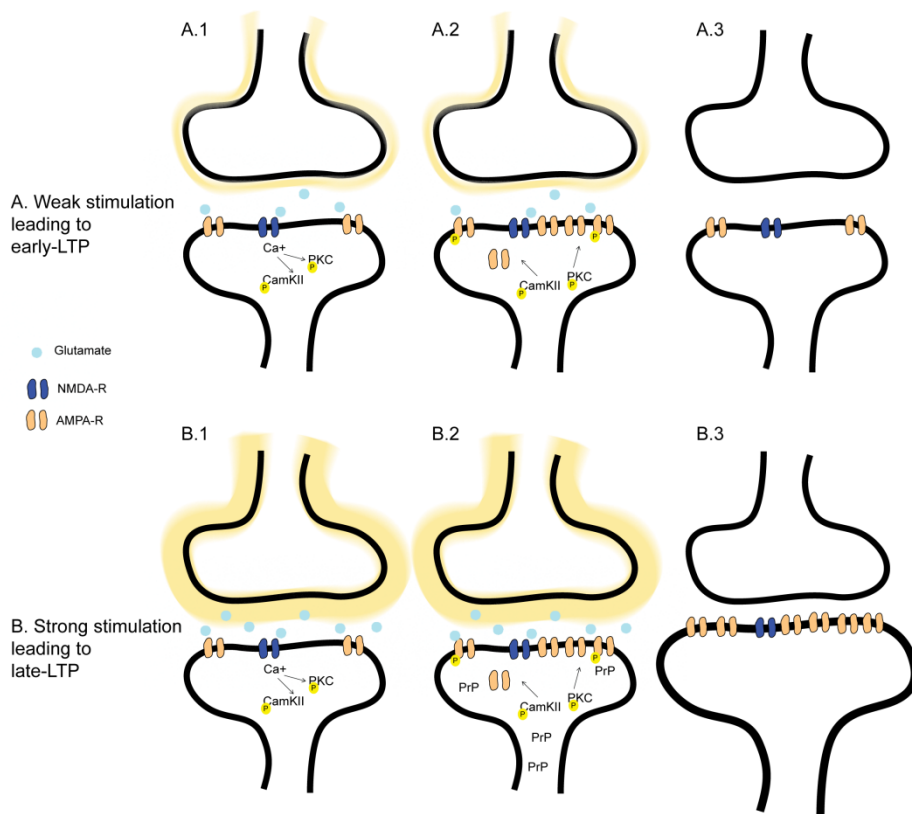


Figure 1: Cellular Consolidation. A.1 Weak stimulation of a pre-synaptic neuron leads to the release of Glutamate and activation of AMPA and NMDA receptors in the post-synaptic neuron. A.2 The resulting Ca^{2+} influx activates CamKII and PKC, which in turn phosphorylate existing AMPA receptors and integrate new ones as well. A.3 If not stabilized by protein production, this potentiation – early LTP – lasts only a few hours after which the synapse returns to its original state. B.1 After strong stimulation, causing more Glutamate release, the same processes occur initially. B.2 Additionally, plasticity-related proteins (PRP) are produced. B.3 This leads to a long lasting, structural (e.g., larger) and functional change of the synapse. If a strong stimulation (as in B) occurs on one synapse but a weak stimulation (as in A) occurs on a nearby synapse of the same neuron, the weakly simulated synapse (A) can hijack some of the PRPs of the other synapse (B). This leads to the long lasting strengthening of the weakly stimulated synapse A.

Typically, the processes associated with early-LTP and late-LTP are synapse-specific in that they unfold in the stimulated spine – but not nearby spines – of the postsynaptic neuron. However, Frey and Morris (Frey and Morris 1998) proposed the "synaptic tagging and capture hypothesis" to model how early-LTP that is destined to degrade at one synapse can be transformed to late-LTP by the strong tetanisation of a different, nearby synapse on the same neuron. Weak tetanisation (too weak to induce late-LTP but strong enough to induce early LTP) at synapse A theoretically leads to the setting of a "tag", which may, for example, consist of the introduction of new AMPA receptors in the synapse. On its own, this "tag" will not become stabilized because the biochemical cascade leading to protein synthesis at that synapse will not occur. However, strong tetanisation shortly before or after the weak event at a separate synapse of the same cell will lead to the setting of its own "tag" and also to the synthesis of plasticity-related-proteins (PRP). These PRPs now not only stabilize the "tag" of the strongly tetanised synapse but can also be "hijacked" by the tag of the weakly tetanised synapse, which is thus stabilized as well (Redondo and Morris 2011). In a series of experiments, they and others went on to show that dopamine plays an important role for the persistence of memory by inducing PRPs (Redondo and Morris 2011; Rossato et al. 2009; Wang et al. 2010).

Synaptic tagging and capture was subsequently translated to *behavioural* tagging. Behavioural tagging is said to occur when a weak and otherwise transient memory is transformed into a more durable memory when it occurs close in time to other behaviourally relevant experiences that provide PRPs (Moncada et al. 2015). For example, Wang et al (2010) showed that exposure to a novel event shortly before or after a hippocampal-dependent, weak, spatial encoding experience, allowed the originally weak memory to last much longer. In parallel electrophysiological and behavioural experiments, they showed that this memory enhancement was dependent on dopamine and protein synthesis. For a tagging and capture effect to be seen, both events or tasks have to rely on the same brain area, contain overlapping neuronal populations and the events have to occur in close temporal proximity, usually within a 1-2h window surrounding the weak event (Moncada et al. 2015; Wang et al. 2010). In conceptually related behavioural tagging work, Dunsmoor et al. (2015) found that weak memories of incidentally presented items from a semantic category (e.g., animals or tools) could be retroactively and selectively strengthened if other items from that same category were made emotionally salient shortly thereafter by pairing them with shock (an amygdala-dependent Pavlovian fear-conditioning task). The retroactive enhancement of the weakly encoded items was not observed on an immediate recognition test but only emerged following a period of consolidation. This finding is consistent with prior work showing that the amygdala can influence the post-training consolidation processes in the hippocampus (McGaugh 2004) (see also Chapters by Cunningham and Payne and by Meir Drexler and Wolf) but is the first to show that this effect can be selective (occurring only for previously encoded items that are related to the emotionally conditioned items).

On the surface, these findings are surprising because, usually, two tasks or experiences that occur in close proximity will show detrimental retroactive interference effects on memory for the first event instead of a strengthening of memory. In other words, on the surface, synaptic tagging almost seems to deny retroactive interference, but it doesn't really. There are times when subsequent memories interfere and times when they enhance, but the details matter. It seems to be the case that enhancement occurs when one memory is weak and the other is strong. In that case, the weak memory is enhanced even if the strong event occurs shortly after the weak event. Under other conditions, such as when two strong memory events occur in succession, interference might occur. Studies indicate that competition for protein resources between different learning tags is one of the main factors that give rise to memory interference (Moncada et al. 2015).

Systems Consolidation

Memories initially dependent on the hippocampus are thought to become less dependent on the hippocampus over time and to instead rely more on cortical representations. This process of memory reorganization is termed systems consolidation. Initial evidence for systems consolidation came from patients with hippocampal lesions (Scoville and Milner 1957), and this evidence was later confirmed by experimental studies using artificially induced hippocampal lesions in animals (for review see Squire et al. 2015; Zola-Morgan et al. 1994); in addition to an impairment in the encoding of new memories, these subjects displayed a retrograde memory deficit with a very characteristic temporal gradient: more recent memories were lost while older memories remained intact. Over the past decades, a multitude of studies have investigated this phenomenon in an effort to uncover its underlying mechanisms. The weight of evidence suggests that the hippocampus initially binds the details of our daily experiences that are initially recorded by independent neocortical regions.

However, it only serves a temporary role (Morris 2006). The hippocampus is thought to establish connections between these neocortical regions, allowing the newly learned information to be assimilated into existing neocortical networks without causing interference and at the same time extracting the salient information and compressing the memory when necessary (Battaglia et al. 2012; Frankland and Bontempi 2005). These memories are not “transferred” from the hippocampus to the cortex; instead the memory engrams in the cortex are already established during the encoding experience and only need to be linked together to enable retrieval without hippocampal assistance.

Lesburguères et al (2011) presented initial evidence for an AMPA- and NMDA receptor dependent “tagging process” in the cortex during encoding, which was crucial for the progressive hippocampal-driven rewiring of cortical networks supporting remote memory storage. In a seminal study Cowansage et al (2014) then went on to show that when such neural ensembles in the retrosplenial cortex are activated by optogenetic techniques, memory retrieval can occur even with hippocampal inactivation at a time point when sensory cues are not sufficient for memory retrieval without hippocampal involvement (i.e., when the memory is still hippocampal dependent). Both of these studies used tasks that were novel for the animal. With previous knowledge of the task, cortical representations during encoding become even more important. For example, after rats have learned a map of flavour-location associations over a period of weeks to months, a new paired-associate can be learned and integrated into the known map in one single trial and induce plasticity-related gene expression in the prefrontal cortex (Tse et al. 2011). Further, this previous knowledge, most likely represented in an extended cortical network, now allows for systems consolidation to occur at a much more rapid pace. Classically, weeks to months are needed for a memory to become independent of the hippocampus, but when previous knowledge in form of a schema is present, this process can be completed in 24-48h (Tse et al. 2007). These studies, together with human experiments (van Buuren et al. 2014; van Kesteren et al. 2010a; van Kesteren et al. 2010b; van Kesteren et al. 2012; Wagner et al. 2015), suggest that the prefrontal cortex has a special importance when new information is learned in the context of previous knowledge, perhaps by binding the information distributed across other brain areas (see also Chapters by Fernandez and by Genzel and Battaglia). While in this case schemas allowed for rapid consolidation, initially, during learning, the hippocampus was still needed (Bethus et al. 2010; Tse et al. 2007).

Conceivably, when cortical schemas are extensive enough and are harnessed during encoding, the hippocampus may not even be needed during initial learning. For example, during rapid word learning, words are *fast mapped* onto new concepts, an important learning mechanism during vocabulary building in childhood. During “normal”, explicit word learning, lists are presented to be “learned” by the subjects. In contrast, during *fast mapping*, subjects are not explicitly asked to learn a new word; instead, the word is introduced in context with a known item and its meaning is apparent through inference (Coutanche and Thompson-Schill 2015). For example, instead of presenting a picture of a new animal with the name of the animal, the subject would be shown the new animal together with a known animal and asked “Is the tail of X pointing down?” Studies have shown that this type of learning leads to rapid integration into cortical networks (Coutanche and Thompson-Schill 2014) and may not need the hippocampus even during the encoding experience (Sharon et al. 2011); however the latter finding is still controversial because efforts to replicate it have not been successful (Greve et al. 2014).

We are usually awake when we learn something new, but systems consolidation may take place mainly during sleep (see Chapters by Schönauer and Gais, by Rauss and Born and by Kreutzmann and colleagues), most likely because, during sleep, no new experiences can interfere with the process. Two mechanisms have been proposed to act during sleep: memory replay and synaptic scaling. These mechanisms are thought to act together to enable the extraction of salient features and integration into cortical networks (Genzel et al. 2014). “Replay,” is the reactivation of patterns of network activity that had occurred during previous experience and is thought to lead to potentiation of relevant synaptic connections in the cortex (see also Chapter by Zhang, Deuker and Axmacher). “Scaling” refers to “...sleep homeostatically but nonspecifically regulating synaptic weights to improve the signal-to-noise ratio of memory traces” (Tononi and Cirelli 2006; Tononi and Cirelli 2014). The combined “push–pull” action of replay on the one hand (“push” equals potentiating “important” traces) and scaling on the other (“pull” equals weakening irrelevant traces) may together aid the construction and updating of memory networks in the cortex (Diekelmann and Born 2010; Genzel et al. 2014; Lewis and Durrant 2011).

Non-REM sleep (NREM) is especially important for systems consolidation of memories, with replay occurring throughout NREM and scaling becoming more dominant during deeper NREM also known as slow wave sleep (for the role of REM sleep in memory consolidation see (Genzel et al. 2015c)). Different oscillations have been shown to play specific roles in these processes (see also Chapters by Bergmann and Staresina and by Maier and Kempster). Replay is initiated by a slow oscillation (0.5-1Hz, seen as K-complex in the surface EEG) in the prefrontal cortex, which travels to the medial temporal lobe, where it is followed by a sharp-wave-ripple (100-200Hz) in the hippocampus (Figure 2). During the sharp-wave-ripple replay can be measured in the hippocampus and prefrontal cortex; this replay is then followed by a sleep spindle (13-16Hz) (see also Chapter by McDevitt and colleagues) deafferenting the prefrontal cortex from the hippocampus perhaps to enable integration into pre-existing networks (Genzel et al. 2014; Peyrache et al. 2011; Peyrache et al. 2009; Sullivan et al. 2014). Interestingly, motor cortex replay after motor sequence learning is seen later on in this oscillatory sequence, with replay occurring during, not before, the spindle (Ramanathan et al. 2015), even though this type of learning has been shown to involve the hippocampus (Genzel et al. 2015a; Schendan et al. 2003). Perhaps these two types of replay represent different mechanisms, or perhaps the delay is caused by the time that is needed for the information to travel across the cortex (Buzsaki 2015; Genzel and Robertson 2015). Replay can be measured in many brain areas (hippocampus (Wilson and McNaughton 1994), striatum (Pennartz et al. 2004), VTA (Gomperts et al. 2015), olfactory/prefrontal/visual/motor cortex (Barnes and Wilson 2014; Ji and Wilson 2007; Peyrache et al. 2009; Ramanathan et al. 2015; Yang et al. 2014) and disrupting sharp-wave-ripples and thus replay during sleep leads to a deficit in hippocampal led consolidation (Ego-Stengel and Wilson 2010; Girardeau et al. 2009), providing further evidence for the importance of sleep in systems consolidation. After replay strengthens important memory traces during early stages of NREM, scaling in the cortex is thought to occur during delta-waves (1-4Hz) during deeper NREM.

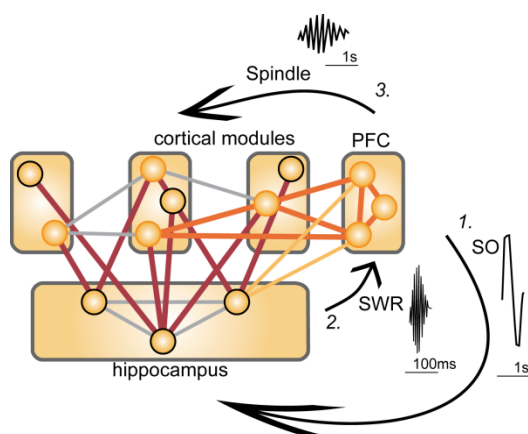


Figure 2: Systems Consolidation during Sleep. Memory replay during NREM sleep is initialized by a slow oscillation (SO) traveling from the prefrontal cortex (PFC) to the medial temporal lobe and the hippocampus (1). There it is followed by a sharp-wave-ripple (SWR) and the reactivation of hippocampal and PFC neural ensembles of new memories (2). Subsequently, the sleep spindle can be seen in the cortex (3), deafferenting the PFC from the

hippocampus, and accompanied by memory replay events farther along the cortex. Adapted from (Genzel and Robertson 2015)

Neural replay and related consolidation processes may preferentially unfold during periods in which no new information is being actively encoded (Mednick et al. 2011). NREM sleep is obviously one such period, but neural replay has also been found to occur during periods of quiet wake (Karlsson and Frank 2009). Indeed, in various kinds of learning tasks, post-learning wakeful resting has yielded effects on the consolidation of memory that are similar to the effects associated with NREM sleep (Dewar et al. 2012; Tambini et al. 2010). There seem to be three types of sharp-wave-ripple related memory replay, during the task, quiet rest and sleep; each contributing to memory but perhaps in a slightly different way (Dupret et al. 2010). Replay during task execution has been related to working memory (Jadhav et al. 2012) and replay during quiet rest seems to stabilise the hippocampal memory trace (Dupret et al. 2010). Some evidence suggests that only during sleep does replay occur in the cortex as well as the hippocampus (Peyrache et al. 2009; Ramanathan et al. 2015). This systems-wide replay during sleep may be due to increased cross-brain connectivity seen during light NREM in comparison to wake (Spoormaker et al. 2011). Then again, other evidence suggests that coordinated reactivation between the hippocampus and cortex may also occur during the awake state. For example, using fMRI, Tambini et al. (2010) found that following an associative learning task, enhanced hippocampal-cortical interactions occurred during subsequent rest, and the magnitude of resting correlations across subjects predicted individual differences in later associative memory for the previously learned items. Thus, exactly how consolidation processes differ between the sleep and awake states remains an open question. Nevertheless, at a minimum, it seems reasonable to suppose that most systems consolidation occurs during sleep, if no other reason than much of the awake state involves the active encoding of new information (Buzsaki 1989).

Interaction of cellular and systems consolidation

Most discussions of cellular and systems consolidation treat them separately, as if they are independent from each other. Further, in mammals, cellular consolidation is also often used as a synonym for consolidation occurring in the hippocampus, since it is the classic brain area used for investigation of this process. Of course, the picture is more complex (Mednick et al. 2011). Only those memories initially stabilized in the hippocampus via cellular consolidation will survive long enough for systems consolidation to occur in the following sleep periods (Dupret et al. 2010). Furthermore, cellular consolidation is needed in the cortex directly after encoding (Lesburgueres et al. 2011; Tse et al. 2011) as well as later on for systems consolidation to be effective. Instead of viewing cellular and systems consolidation as separate entities, we need to focus more on their interactive dynamics. Interestingly, while a minimum amount of cellular consolidation in the hippocampus is needed for later systems consolidation, too much of the former can actually inhibit the latter. Very novel events lead to very large dopamine release in the hippocampus via pathways from the VTA and LC, enabling very strong cellular consolidation. This seems to “tag” memories to remain hippocampal with its more detailed memory representation and inhibits systems consolidation to occur in later sleep phases (Genzel et al. 2015b). In humans this form of memory is known as flashbulb memory.

Although the standard model holds that all declarative memories eventually become independent of the hippocampus (Figure 3A), some memories, even though they may undergo systems consolidation, never become fully hippocampal independent. For example, while spatial memory learned in the watermaze shows signatures of cortical consolidation (Genzel et al. 2015b), most findings indicate that the hippocampus is always needed for retrieval (for review see Squire et al. 2015). This may be due to navigational issues during swimming, since similar dry land tasks usually become independent of the hippocampus and if a schema is present even at a rapid time-scale (Tse et al. 2007) (Figure 3B). In other well-controlled animal studies, the temporal gradient of retrograde amnesia is also not always observed even on tasks that do not have an obvious spatial navigation aspect (e.g. context fear conditioning, (Broadbent and Clark 2013)), however the reasons for the empirical variability are not well understood. The transformation theory (former Multiple Trace Theory) argues that detail-rich, episodic memories remain dependent on the hippocampus (Nadel and Moscovitch 1997) (Figure 3C) (see also Chapters by Sekeres, Moscovitch and Winocur and by Cheng). However, this view remains controversial because patients with bilateral damage limited to the hippocampus generally do not exhibit the profound and selective loss of episodic memories that has been strikingly apparent in patients with more extensive cortical damage, such as Patient K.C. (Squire et al. 2015). Further, just because a memory can be retrieved when the hippocampus is lesioned, does not mean that the hippocampus is not involved when intact (Axmacher et al. 2009). Technical and methodological issues may also play a role. Studies have shown that using inactivation methods with different time scales (optogenetics, pharmacology, permanent lesions) leads to different results (Goshen et al. 2011; Otchy et al. 2015), which may be due to a time-lag in compensatory mechanisms (Goshen et al. 2011) or negative effects of transient manipulations on downstream circuits (Otchy et al. 2015).

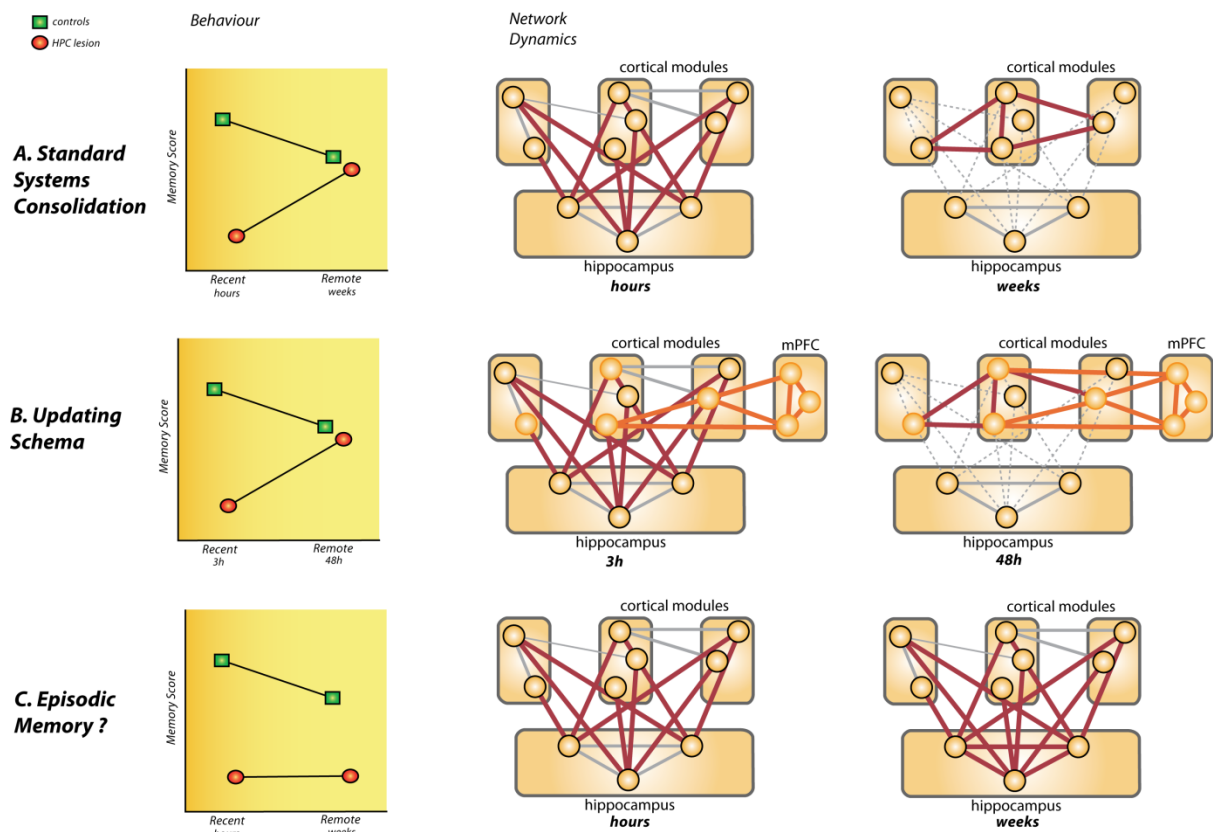


Figure 3: Systems Consolidation. A. According to the standard model, the classic retrograde consolidation gradient in hippocampal lesioned animals shows that while memories are initially hippocampal dependent over time (weeks to months) the cortical network is eventually strengthened to be sufficient for memory recall. B. When a schema, in form of a cortical network of relevant information, is present, this process occurs at a rapid rate (within 48h). C. Some memories never seem to become hippocampus independent. The transformation theory proposes that these represent episodic memories that always rely on the detailed representation in the hippocampus. Adapted from (Squire et al. 2015).

Conclusion

The idea that memories consolidate began as a simple concept: the physiological processes associated with encoding persevere for a limited period of time, thereby rendering the memory trace more resistant to retroactive interference than it otherwise would be (Müller and Pizecker 1900). After more than a century of research, one thing has become abundantly clear: consolidation is not a simple process. Our understanding of how consolidation works – and our awareness of how much we still do not know about it – have both increased enormously. Many of the intricate details of the cellular consolidation process have now been deciphered, but critical details are still largely unknown. In particular, how those cellular processes trigger the later processes that theoretically underlie systems consolidation – namely, neural replay and the associated exchange of information between the hippocampus and neocortex – remain mysterious. Fortunately, the tools needed to advance our understanding of what remains to be discovered are becoming more powerful than one might have hoped (or even imagined) only a few years ago. It therefore seems safe to assume that the remaining secrets of the memory consolidation process will be exposed sooner rather than later.

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