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Nikolai Axmacher
Björn Rasch *Editors*

Cognitive Neuroscience of Memory Consolidation

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Introduction

Memory is a fundamental trait underlying adaptive behavior. Only if previous experiences can be stored and used to influence and alter future behavior, adaptation with respect to the environment and environmental changes is feasible. Thus, the capacity to store memories exists in the vast majority of living organisms, starting from simple cell forms to highly complex organisms including animals and humans. And as the ability to store memories is also the prerequisite to develop consciousness, self-awareness, and personality, memory and its underlying mechanisms have fascinated researchers ever since.

The formation of memories is typically separated into different phases. The initial phase always requires the encoding of information by the organism. And as we still do not have any other means to identify the successful formation of a memory, some types of retrieval processes are also necessarily involved. In this book, we specifically focus on the time period between encoding and retrieval: What mechanisms are involved *after* the successful encoding of information?

One major advancement in understanding the mechanisms underlying long-term formation of memories was the proposition of a consolidation process. In 1900, Müller and Pilzecker proposed that after successful encoding, a physiological process "perseverates" and stabilizes encoded memory representations (Lechner et al. 1999; Müller 1900), gradually rendering them less susceptible to future interferences caused, e.g., by new learning. Since then, tons of evidence in favor of the consolidation of memories has been provided by very different research areas, including the fact that long-term memory retention initially depends on the synthesis of new proteins, whereas it does not any more after a certain period of consolidation (Dudai 2004; Kandel 2001). In addition, temporally graded amnesia was observed in patients with hippocampal damage (Squire and Wixted 2011). Furthermore, pharmacological studies in animals show that certain manipulations are only effective shortly after encoding, but not after a period of consolidation (McGaugh and Izquierdo 2000). Based on these studies, McGaugh (2000) proposed in his seminal review paper "a century of consolidation," that there are probably different waves of memory consolidation after their encoding, initially including cellular stabilization processes but involving also large-scale changes in the

organization of the memory trace (i.e., systems consolidation, see Dudai 2004). And even after the successful consolidation of a memory, retrieving a memory can under certain circumstances render these memories again instable and susceptible to interfering influences, requiring a period of reconsolidation in order to persist (Nader and Hardt 2009).

In spite of the overwhelming experimental support for consolidation processes from neuroscientists, cognitive psychologists have been quite skeptical whether such a process indeed exists. On the one side, the skepticism was due to the failure to find consistent evidence that memories become more resistant to interference by new learning with time (see Wixted 2004, for an overview). Thus, forgetting by either interference, decay, or a combination of both were (and still are) the prominent concepts in cognitive psychology instead of memory consolidation. On the other side, cognitive memory researchers did not have the appropriate methodological approaches to study this process, as the cognitive processes underlying memory consolidation cannot be directly observed. The bridging of this gap started with the emergence of studies in the cognitive neurosciences that combine cognitive testing with neuroimaging recording and stimulation technique during off-line periods such as sleep. In these studies, several important concepts, including, for example, the functional role of brain oscillations and spontaneous memory reactivation during off-line periods, have been put forward to characterize the physiological processes of memory consolidation and to link them to putative behavioral measures of consolidation. The goal of this book was to give an overview of the state of the art of this endeavor, based on the contributions from leading cognitive neuroscientists who summarize recent advances in the exciting research field of the cognitive neuroscience of memory consolidation.

The book is organized into five parts: In the first part, conceptual questions of memory consolidation and its effect on the reorganization of memory systems are presented. Chapters in the second part describe more closely the processes of memory consolidation in animals and humans, emphasizing the role of sleep. Contributions in the third part describe the mechanisms of memory consolidation on the level of systems physiology or neural networks, focusing on oscillations and replay. In the fourth part, several factors are introduced which modulate memory consolidation during waking and sleep. Finally, the last part translates concepts of memory consolidation to clinical populations.

Part I: Conceptual Questions of Memory Consolidation

More specifically, in the first part, Genzel and Wixted provide an overview of the concepts and empirical foundations of cellular and systems consolidation. With respect to cellular consolidation, they introduce synaptic long-term potentiation (LTP) as a putative neural mechanism as well as the concepts of synaptic and behavioral “tagging.” On the system level, they discuss a specific role of sleep and

sleep-related oscillations, replay and scaling as well as prior knowledge on system consolidation processes. Adopting an alternative perspective on memory consolidation (called the "Trace Transformation Theory"), Sekeres, Moscovitch, and Winocur argue that the hippocampus is uniquely suited to promote pattern separation and is required to support a very specific, context-dependent form of memory. By contrast, neocortical areas—in particular in medial prefrontal cortex and anterior cingulate cortex—may only support memory for a context-independent, generalized representation of an event, its "gist." In this framework, they also describe how memory traces may be reorganized following their reactivation and how this could be related to memory reconsolidation. In the next chapter, Fernandez capitalizes on the important role of the medial prefrontal cortex in memory consolidation: Lesion experiments in animals, neuropsychological studies in patients, and neuroimaging research in healthy participants provide converging evidence that while newly acquired memory traces are dependent on the hippocampus, consolidation transfers this role to the medial prefrontal cortex. This is further explained by the relevance of the medial prefrontal cortex for the control of schema-congruent knowledge that is extracted from individual episodes during memory consolidation. Finally, Cheng introduces a third alternative to the standard consolidation theory and the multiple trace theory: He assumes that episodic memory traces remain always hippocampus-dependent. However, he further argues that semantic learning exploits hippocampal traces, and that autobiographical memory may be based to different degrees on hippocampal episodic memory or neocortical semantic information. As a result, consolidated information may appear hippocampus-independent when it is largely based on such semantic information.

Part II: Memory Consolidation During Off-Line Periods and the Role of Sleep

In the second part on the role of sleep in memory consolidation, Kreutzmann, Tudor, Angelakos, and Abel review which signaling pathways related to the consolidation of hippocampus-dependent memories are impaired by sleep deprivation after learning in rodents. They discuss that the timing of sleep deprivation is crucial and highlight its effects on molecular mediators of synaptic plasticity as well as on the expression and translation of genes that are relevant for learning and memory. Remaining in non-human animal models, Wilson, Kondrakiewicz, and Barnes specifically discuss the consolidation of odor memories and the influence of sleep on this process. They first review the anatomy and physiology of the olfactory system in both vertebrates and invertebrates and describe different types of odor memory. Afterward, they discuss how processing in the piriform cortex changes during different sleep stages and how their prominent features affect odor memory consolidation, considering various vertebrate and invertebrate species. Turning to humans, Schönauer and Gais describe evidence that sleep benefits the consolidation

of different memory systems, including declarative, procedural, and emotional memory. After summarizing studies showing the effects of sleep on each of these systems separately and the presumed mechanism underlying this effect—reactivation—they discuss how memory systems interact and how consolidation may affect this interaction. In the next chapter, Rauss and Born emphasize that not all memories are equally consolidated during sleep, but rather those which are relevant for future behavior. They propose that memory consolidation during sleep mainly serves to optimize predictive coding of upcoming events, i.e., generating expectations about regularities in the world. They demonstrate how previous studies (e.g., on gist abstraction and language learning during sleep) can be interpreted within this novel framework and discuss open questions for future research. As emotional events are also highly relevant for future behavior, Cunningham and Payne first describe that the amygdala plays a critical role for facilitating consolidation of emotional memories over long time periods. Next, they review the role of sleep (particularly REM sleep) for the consolidation of emotional memories and discuss the physiological processes supporting this relationship, such as high levels of amygdala activity and acetylcholine. If memory consolidation is facilitated by sleep, is it related to dreaming? In their chapter, Eichenlaub, Cash, and Blagrove discuss which events during daily live are incorporated into dream contents. They first review studies indicating that in particular very recent events from the 1–2 days before a night of sleep and those around 5–7 days earlier are incorporated, and then describe that emotionally laden events often become part of dreams. Finally, they critically discuss arguments for and against the view that dreaming is related to memory consolidation. Along similar lines, Schredl reviews studies suggesting that cueing during REM sleep may increase the likelihood that dream contents are related to the events associated with the cues before sleep. Furthermore, he describes evidence that waking contents are incorporated into dreams, and then reports results that dreaming may improve subsequent performance, suggestive of a functional role of dreams. Finally, he reviews studies about possible positive effects of lucid dreaming and suggests future research topics in this area.

Part III: Mechanisms of Memory Consolidation on a Systems Physiology Level

The third part specifically focusses on neural mechanisms of memory consolidation during sleep and wakefulness on a systems physiology level. Bergmann and Staresina capitalize on the role of neural oscillations—in particular, slow oscillations, sleep spindles, and ripples—for memory consolidation. Summarizing work in both animals and humans, they describe both the physiological mechanisms and the putative functional role of these oscillations for hippocampal–neocortical interactions. They then discuss if and how these oscillations support the reactivation of previously acquired memory traces during sleep. Focusing on sleep spindles,

McDevitt, Krishnan, Bazhenov, and Mednick review their putative physiological basis and discuss how sleep spindles are related to the consolidation of different memory systems. They first describe correlational studies and then pharmacological manipulations showing that sleep spindles are functionally related to consolidation processes during sleep. In their chapter on hippocampal ripples and sharp waves, Maier and Kempter review their putative functional role for memory consolidation and discuss different models on their physiological generation. Their conclusion is paradigmatic for the active yet still emerging field of neural oscillation research: "Despite the huge amount of available data on SWRs and their likely physiological relevance, the basic mechanisms underlying this phenomenon remain largely enigmatic, both *in vitro* and *in vivo*." Hippocampal ripples are typically associated with memory reactivations or "replay." In their chapter, Zhang, Deuker, and Axmacher review the current evidence for replay of stimulus-specific memory traces, or "engram patterns," in humans. They describe evidence both for the existence and for the behavioral relevance of replay in fMRI experiments and then again emphasize the large remaining gaps in our understanding of replay: What is the role of sleep for replay, how is it related to hippocampal ripples, and is it actually causally relevant? Turning back to the system level, the chapter by Genzel and Battaglia capitalizes on the role of the prefrontal cortex in sleep-related memory consolidation. They describe the relationship between sharp wave-ripple complexes and replay, both in the hippocampus and in the neocortex, and discuss their relationship to synaptic plasticity. In particular, they provide evidence that replay in prefrontal cortex is related to hippocampal replay and associated with specific processes at the behavioral, neural oscillation, and neuromodulation level.

Part IV: Modulation of Memory Consolidation

The fourth part deals with important modulators of memory consolidation during wakefulness and sleep. In the first chapter of this part, Meir-Drexler and Wolf emphasize the role of stress for memory, which strongly depends on the memory phase: While stress impairs memory retrieval, it typically improves memory consolidation. The authors discuss the inverse effects of different stress levels and durations and review how extreme stress—trauma—may induce symptoms of posttraumatic stress disorder such as intrusions and flashbacks. In the next chapter, Campos-Beltrán and Marshall focus on the application of weak electric fields for modulating memory consolidation. They first describe how finite element modeling can be used to estimate the effects of artificially applied electric fields on cognitive and physiological processing. They then summarize results from meta-analyses on the impact of these electric fields on declarative and procedural memory consolidation in humans and animals. The contribution of specific pathways in memory consolidation and/or brain rhythms is presented based on studies using optogenetic stimulation. Talamini then describes how the causal relevance of

consolidation-related neural processes can be tested. She first summarizes previous studies which either modulated sleep-related oscillations via electric stimulation or used olfactory or auditory cues to enhance reactivation of specific memory traces. She then describes very recent approaches that target reactivating cues to specific phases of slow oscillations during sleep. These approaches enhance the effects of stimulation on memory consolidation and may be relevant for various applications during health and disease. More specifically, Shanahan and Gottfried discuss previous studies using olfactory cueing to probe memory consolidation. After reviewing studies that investigated the role of cueing on consolidation of declarative memories, they describe the effect of cueing on emotional memory consolidation and other consolidation-related processes such as creative problem solving. Finally, they review studies that used other cueing modalities (such as auditory cueing) and describe burning questions for future research. Following up on auditory cueing, Schreiner, Lehmann, and Rasch describe the potential of sleep and targeted memory reactivation during sleep for language learning. They first summarize studies providing evidence for a benefit of sleep for language learning, and then describe how auditory cues like words presented during sleep can improve central aspects of language learning. They finish with a discussion of the potential oscillatory mechanisms of successful memory reactivation during sleep.

Part V: Clinical Translation

The last part focusses on the clinical aspects of memory consolidation. In particular, reconsolidation might open a window of opportunity to destabilize already consolidated, but non-adaptive memories. Interfering with reconsolidation is clinically beneficial when memories are pathological, as in the case of posttraumatic stress disorder (PTSD). This novel translational approach is described by Kessler, Blackwell, and Kehyayan. They first review research on reconsolidation and then summarize evidence that PTSD can be conceptualized as a disorder of memory. Then, they describe novel studies showing that interference with reconsolidation may indeed reduce the core symptoms of PTSD, intrusions, and flashbacks. While memory traces of traumatic events should be weakened, it would be helpful to augment the influence of experiences made during psychotherapeutic treatment. Novel research has shown that sleep after therapy plays an important role here. These studies and their underlying rationale are discussed by Nissen, Kuhn, Hertenstein, and Landmann. The authors suggest that psychotherapy can be conceptualized as a learning process which either strengthens or reorganizes existing memory traces, and describe putative neural correlates of this learning process. They distinguish between the effects of different sleep stages on either the strengthening or the reorganization of memories. Finally, they discuss whether manipulations of sleep-related consolidation processes after psychotherapy may further augment the therapeutic impact. The final chapter deals with the

phenomenon of "accelerated long-term forgetting," which may occur in temporal lobe epilepsy patients. Baker and Zeman were among the first to describe accelerated long-term forgetting. In their chapter, they review the development of this concept, suggest methodological guidelines to measure accelerated long-term forgetting in a clinical setting, and discuss whether early or later consolidation stages are affected. Finally, they describe the dependence of accelerated long-term forgetting on sleep and its occurrence in different clinical conditions, and consider various underlying mechanisms.

Together, these chapters provide compelling evidence that the field of memory consolidation is actively flourishing, and we thank all authors for their insightful contributions. The concept of memory consolidation bridges a wide range of research areas from cellular and systems physiology via cognitive neuroscience and psychology to clinical applications. With further conceptual and methodological developments, we anticipate more exciting findings to emerge in the near future, which will eventually lead to a deeper understanding of this fundamental yet complex phenomenon.

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Part I
Conceptual Questions of Memory Consolidation

Cellular and Systems Consolidation of Declarative Memory

Lisa Genzel and John T. Wixted

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.

Keywords Memory · Consolidation · Synaptic · System · Hippocampus

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

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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-potentiation (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 (Fig. 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.

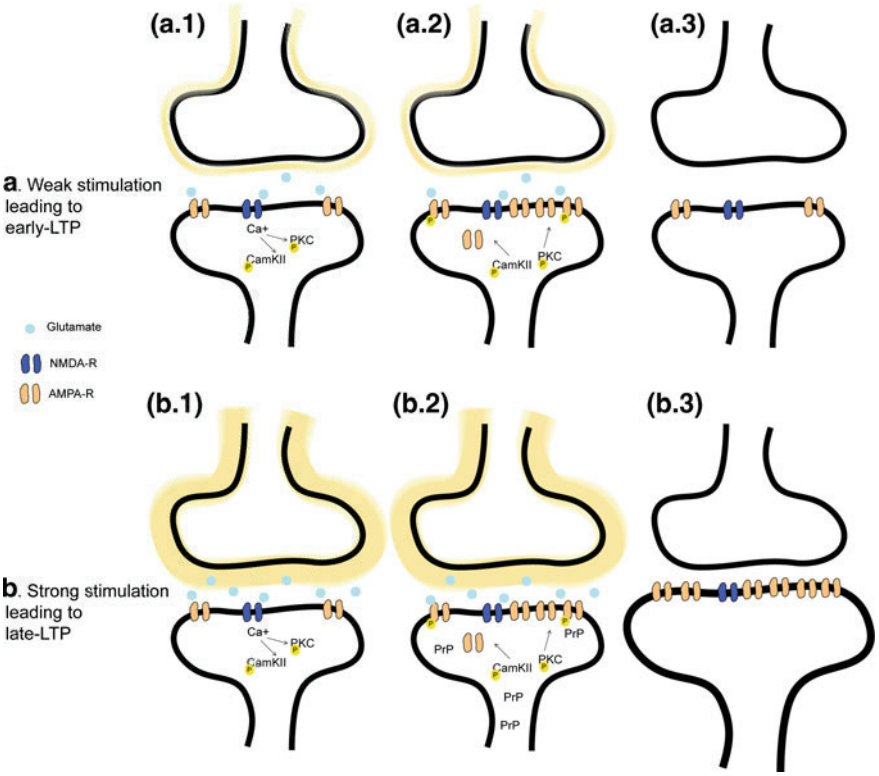

Fig. 1 Cellular consolidation. *a.1* Weak stimulation of a pre-synaptic neuron leads to the release of Glutamate and activation of AMPA and NMDA receptors in the post-synaptic neuron. *a.2* The resulting Ca+ influx activates CamKII and PKC, which in turn phosphorylate existing AMPA receptors and integrate 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**

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).

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 (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 1–2 h 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 24–48 h (Tse et al. 2007). These studies, together with human experiments (van Buuren et al. 2014; van Kesteren et al. 2010a; b; 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, 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 Kempter). Replay is initiated by a slow oscillation (0.5–1 Hz, 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 (100–200 Hz) in the hippocampus (Fig. 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 (13–16 Hz) (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. 2009, 2011; 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.

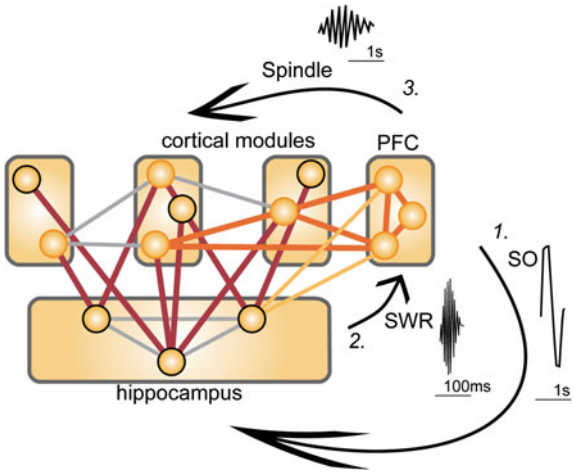

Fig. 2 Systems consolidation during sleep. Memory replay during NREM sleep is initialized by a slow oscillation (*SO*) traveling from the prefrontal cortex (*PFC*) to the medial temporal lobe and the hippocampus (*1*). There it is followed by a sharp-wave-ripple (*SWR*) and the reactivation of hippocampal 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)

After replay strengthens important memory traces during early stages of NREM, scaling in the cortex is thought to occur during delta-waves (1–4 Hz) during deeper NREM.

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 (Fig. 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) (Fig. 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

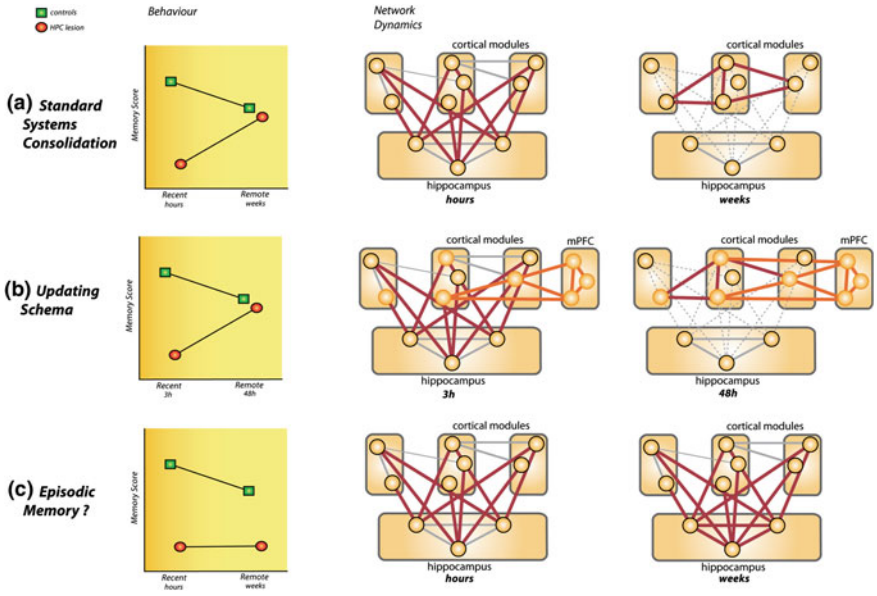

Fig. 3 Systems consolidation. **a** According to the standard model, the classic retrograde consolidation gradient in hippocampal lesioned animals shows that while memories are initially hippocampal dependent over time (weeks to months) the cortical network is eventually strengthened to be sufficient 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 48 h). **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)

remain dependent on the hippocampus (Nadel and Moscovitch 1997) (Fig. 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).

Conclusion

The idea that memories consolidate began as a simple concept: the physiological processes associated with encoding perseverate for a limited period of time, thereby rendering the memory trace more resistant to retroactive interference than it otherwise would be (Müller and Pilzecker1900). 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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