Dual Perspectives

Dual Perspectives Companion Paper: Sleep Is for Forgetting, by Gina R. Poe

Sleep to Remember

Susan J. Sara[1,2,3,4]

[1]Center for Interdisciplinary Research in Biology, College de France, 75005 Paris, France, [2]Centre National de la Recherche Scientifique Unité Mixte de Recherche 7241, 75005 Paris, France, [3]Institut National de la Santé et de la Recherche Médicale U1050, 75005 Paris, France, and [4]Department of Child and Adolescent Psychiatry, New York University Medical School, New York, New York 10016

Scientific investigation into the possible role of sleep in memory consolidation began with the early studies of Jenkins and Dallenbach (1924). Despite nearly a century of investigation with a waxing and waning of interest, the role of sleep in memory processing remains controversial and elusive. This review provides the historical background for current views and considers the relative contribution of two sleep states, rapid eye movement sleep and slow-wave sleep, to offline memory processing. The sequential hypothesis, until now largely ignored, is discussed, and recent literature supporting this view is reviewed.

Key words: **locus coeruleus; memory; noradrenaline; REM sleep; replay; slow-wave sleep**

Introduction

Hypnos, the god of sleep, lived on the Island of Lemos, in a cave through which flowed the river Lethe, the river of forgetfulness. Hypnos had a twin brother, Thanatos, the god of death. So it is quite evident from their mythology that the ancient Greeks regarded sleep as a state closely related to death and a state in which memories were likely to be forgotten. According to Aristotle, the sleep state was "a border-land between living and not-living: a person who is asleep would appear to be neither completely non-existent nor completely existent" (Sprague, 1977). Clearly, ancient Greek thought did not attribute any important functional role to the sleep state.

Scientific investigation into the possible role of sleep in memory consolidation began with the early studies of Jenkins and Dallenbach (1924) who reported that subjects who slept immediately after learning had better retention than those who did not sleep. They interpreted the results in terms of sleep protecting the memory from interference likely to occur during awake states. Subsequent years saw a waxing and waning of interest in the role of sleep in memory processing, but accumulated evidence from both human and animal experimentation lends unequivocal support that sleep is somehow important for memory (for a comprehensive review with 1358 references, see Rasch and Born, 2013). Nevertheless, many questions remain concerning the mechanisms by which underlying neural activity particular to specific sleep stages impacts memory performance. This review will provide a historical perspective for understanding current questions and review some recent developments that further our understanding of sleep-dependent memory processing.

Received Jan. 27, 2016; revised June 20, 2016; accepted June 27, 2016.

The authors declare no competing financial interests.

Correspondence should be addressed to Dr. Susan J. Sara, Center for Interdisciplinary Research in Biology, College de France, 12 pl Marcelin Bertelot, 75005 Paris, France. E-mail: Susan.sara@college-de-france.fr.

DOI:10.1523/JNEUROSCI.0297-16.2017

 0270-6474/17/370457-07$15.00/0

REM sleep

The discovery of REM sleep

Jenkins and Dallenbach (1924) and other early researchers did not know that behavioral sleep comprises two distinct brain states: one characterized by high voltage, slow oscillations, known as slow-wave sleep (SWS) and the other by low voltage, mainly desynchronized activity, resembling wakefulness, called rapid eye movement (REM) sleep. Present day interest in sleep as an active state in which memories may be relived and reinforced, dates from the discovery of REM sleep associated with dreams (Aserinsky and Kleitman, 1953; Jouvet and Michel, 1960). This state of sleep was first named paradoxical sleep (PS) because associated activity in the cerebral cortex resembled wakefulness while the subject appeared to be in a deep sleep with total muscle atonia. Most early research focused on dreams related to this sleep stage (for review, see Miller, 1975).

Early rodent studies

Seminal work by Vincent Bloch and collaborators tested the hypothesis that offline memory consolidation occurs during the period of low voltage, high-frequency cortical activity that is the hallmark of PS. They showed that selective deprivation of PS caused learning impairment and memory deficits in rats (Leconte and Bloch, 1970a; Leconte and Bloch, 1970b), lending concrete support to the intuitive notion that memory consolidation took place during this phase of sleep, associated with dreams and a high level of cortical activity. This same group later showed that learning-dependent increases in PS were correlated with the rate of acquisition of a complex maze task (Hennevin and Leconte, 1971). These studies were complemented by many other studies in rodents (Pearlman, 1969; Fishbein, 1971, Smith et al., 1974; Fishbein and Gutwein, 1977), mostly using some version of a selective REM sleep deprivation protocol (for review, see Smith, 1985). This involved constraining the animal on an inverted flower pot surrounded by a pool of water. Muscle atonia accompanying REM sleep caused the animal to fall off the flower pot into

the water, to a rude awakening. Such studies yielded conflicting results and were highly criticized for not controlling for the effect of stress induced by the sleep deprivation methods on subsequent behavioral evaluation of "memory" (for critical reviews with different viewpoints, see Vogel, 1975; Crick and Mitchison, 1983; Horne and McGrath, 1984; Vertes and Eastman, 2000; Siegel, 2001).

Cuing for directed memory consolidation

Using another research strategy to provide support to the hypothesis that REM sleep is a substrate for memory consolidation, Hars and Hennevin (1987) performed a series of experiments in rats in which a cue associated with the learning was presented during subsequent paradoxical sleep bouts. Rats that received a mild ear shock below awakening threshold, which had served as the conditioned stimulus during learning, remembered the avoidance task better when the cue was presented during REM sleep than when it was presented during the awake state (Hars et al., 1985). On the other hand, when the ear shock was presented during SWS sleep, it impaired acquisition of the task (Hars and Hennevin, 1987). These studies were based on the idea that a specific memory was activated by the cue, so as to become labile. The high-frequency cortical activity associated with REM sleep would then promote consolidation of the active network (Sara, 2010). It should be noted that the Hars and Hennevin (1987) experiments used a highly emotional multisession active avoidance task. The results thus support current notions that non-REM (NREM) and REM sleep stages may be involved in consolidation of different types of memories or different aspects of the same memory (Smith, 2001). This new insight has promoted a renewed interest in REM sleep-related memory processes (Llewellyn and Hobson, 2015; Fogel et al., 2015).

REM sleep for consolidation of procedural and emotional memories

There is some evidence that the REM stage of sleep is involved in the consolidation of procedural memory. Procedural memory can best be described as "knowing how" as opposed to declarative memory or "knowing that." Motor skills, such as walking, talking, playing a musical instrument, and skiing, are considered to be based upon procedural memory. These memories involve brain regions other than the hippocampus, are characterized by a very slow acquisition period (sometimes over months or years), and are very persistent, once acquired. Evidence that REM sleep plays a privileged role in motor skill acquisition comes mainly from studies in which the subject is awakened either early in the sleep cycle, sleep that is mostly NREM, or late in the cycle containing "REM-rich" sleep. In this way, it can be shown that memory for procedural tasks is more likely to be disrupted with loss of REM-rich sleep, whereas memory for declarative tasks is dependent on earlier SWS (Plihal and Born, 1997). The weakness of this study lies in the fact that it uses the "split-night" design where there is no EEG control for the time of waking, so the relative amount of REM and NREM sleep deprivation can only be loosely estimated. This study is still highly cited as evidence for a dissociation of the roles of REM and NREM sleep in procedural and declarative memory, respectively. Subsequent supporting evidence is sparse, with Genzel et al. (2009) and Saxvig et al. (2008) failing to find any evidence for a clear dissociation using a carefully controlled protocol with EEG monitoring the stages of sleep. Moreover, there is other direct evidence that SWS and associated sleep spindles play an important role in consolidation of motor skills (Walker et al., 2002; Clemens et al., 2006; Wamsley et al., 2012). Thus, consolidation of procedural memory does not appear to be a specific function of REM sleep.

Evidence for a role of REM sleep in consolidation of the emotional components of memories is stronger, with several recently published studies in humans (for review, see Gilson et al., 2015; Groch et al., 2016; Wiesner et al., 2015; Hutchison and Rathore, 2015). This growing body of literature converges to support the view that "emotional arousal during encoding is beneficial to recall only if REM sleep occurs after learning" (Wiesner et al., 2015).

Mechanisms of memory consolidation in REM sleep

The precise mechanisms by which REM sleep promotes consolidation of emotional memories remains unresolved, although there are some studies suggesting that LTP processes are activated in REM sleep. Ravassard et al. (2015) have shown impairment of both contextual fear conditioning and LTP in the dentate gyrus of the hippocampus after short periods of REM sleep deprivation. In these same studies, an increase in REM sleep is correlated with better retention of the task and stronger LTP.

Hippocampal theta rhythm. There is a large body of literature suggesting that theta oscillations, characteristic of REM sleep, play a role in memory consolidation, particulary in fear conditioning and emotional memories (for review, see Hutchison and Rathore, 2015). Causal evidence has recently been provided by an elegant experiment in which hippocampal theta was suppressed by optogenetically silencing GABAergic neurons in the medial septum, that drive hippocampal theta rhythm (Boyce et al., 2016). Genetically modified mice were injected into the medial septum with a virus delivering the photoinhibitory gene Archaerhodopsin. Mice were subsequently trained in a spatial-object recognition task or a contextual fear conditioning, both dependent on the hippocampus. The septal GABAergic neurons driving hippocampal theta were silenced selectively during each REM sleep episode after the learning session. Compared with various control groups, mice with suppression of REM sleep theta expressed significantly less memory for either task. Importantly, there was no memory deficit in a cued memory recall test that is not dependent on the hippocampus. Thus, theta oscillation in the hippocampus during REM sleep is a necessary condition for consolidation of hippocampal-dependent memories.

Plasticity genes and protein synthesis. The first report of experience dependent upregulation of plasticity related immediate early genes was from Ribiero et al. (1999). Rats were exposed for 3 h to an enriched novel environment, after which they were allowed to sleep and brains states were monitored electrophysiologically. Rats were killed 30 min after a bout of REM sleep, SWS, or wakefulness, and brains were processed by *in situ* hybridization. Rats killed after the REM bout had significantly higher levels of expression of the plasticity- related immediate early gene zif-268 in cortex and hippocampus. Using a similar strategy, this group recently showed upregulation of multiple immediate early genes during REM sleep in the hippocampus, after object recognition learning (Calais et al., 2015).

A study using LTP in the hippocampal dentate gyrus as a model of plasticity revealed waves of upregulation of extrahippocampal zif-268 gene expression during subsequent episodes of REM sleep. The signal was found in more proximal structures, such as amygdala and entorhinal cortex, after the first bout of REM, then propagated to more distal regions in subsequent REM bouts. These results are taken as evidence for an REM sleep-dependent mechanism by which a memory trace originating in the hippocampus propagates to other brain regions. This takes place over many hours through successive bouts of REM sleep. Importantly, inactivation of the hippocampus immediately after

the onset of the REM sleep episode prevents the expression of the zif-268 signal downstream (Ribeiro et al., 2002), suggesting the necessity of the hippocampal signal in initiating the systems-level consolidation process.

SWS and memory

The two stage hypothesis

In his seminal paper, Buzsáki (1989) put forth the hypothesis of a "two stage" memory formation. Information is acquired during wakefulness and exploratory activity when the hippocampus activity oscillates in a theta/gamma mode, during which cortical information is transmitted and weakly potentiated onto CA3 neurons. During offline sleep (or rest), fast oscillations, called ripples, with synchronous population bursts 5–8 times higher than during wakefulness, predominate in CA3 resulting in LTP of the CA1 target synapses and potentiation of hippocampal output to cortex (Buzsáki, 1998). This model was highly influential in refocusing interest in the role of sleep in memory formation, but this time on NREM or SWS.

The model predicts that sequences of neuronal discharges occurring during behavioral exploration should be replayed in a "time-compressed manner" (Buzsáki, 1998). Many publications appeared confirming this prediction (Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996), some showing that the replay of sequences occurs during the sharp wave ripple (SWR) high-frequency oscillation, when a select population of neurons fires at a very high frequency. (Kudrimoti et al., 1999; Atherton et al., 2015).

Cuing in SWS

Replay does not appear to be random. Indeed, presenting specific cues associated with the original learning during subsequent SWS can facilitate memory performance upon awakening, for the auditory modality in rodents (Bendor and Wilson, 2012) and humans (Creery et al., 2015). In the olfactory modality, odors that were part of the learning context, when presented during SWS, memory retention of paired associate learning in humans (Rasch et al., 2007). In a more explicit test of replay during SWS, a recent study in rats used "olfactomimetic" stimulation comprised of electrical pulses to the olfactory bulb (conditioned stimulus), paired with footshock (unconditioned stimulus). When the conditioned stimulus was presented in absence of the unconditioned stimulus during the awake state, extinction occurred; when presented during SWS, the conditioned fear memory was stronger and more accurately tuned to the conditioned stimulus (Barnes and Wilson, 2014). These results together provide strong evidence for a cue-induced bias determining which neuronal ensembles will be replayed during sleep. The phenomenon is in contrast to earlier studies discussed above, where a reminder during sleep impaired subsequent memory performance when administered during SWS, but enhanced it when delivered during the REM state (Hars et al., 1985; Hars and Hennevin, 1987).

Reward, replay, and the noradrenergic system

Reward associated with spatial learning increases the probability of offline replay of ensembles of cells active during spatial exploration (Singer and Frank, 2009). Indeed, rewarded trials induced a fourfold increase in SWR rate associated with the intertrial interval. During epochs where new reward contingencies were learned, the increase in these fast oscillations between trials was even greater. How can the presence of reward on a learning trial influence the probability of SWRs being generated offline? We know that these SWRs are generated by high-frequency synchronous firing of a population of neurons in CA3 region of the hippocampus. Although this occurs most often during SWS, SWRs are also observed during quiet rest periods between learning trials. It is well established that neuromodulatory neurons of the VTA and locus ceruleus (LC), releasing dopamine and noradrenaline (NE), respectively, emit phasic bursts of action potentials in response to primary reward, or to stimuli that predict reward delivery (Sara and Segal, 1991; Schultz, 2001; Bouret and Sara, 2004). So it is reasonable to suppose that, on rewarded trials during spatial learning, dopaminergic and noradrenergic neurons are firing in tandem with place cell ensembles engaged in the learning. This "firing together" during acquisition could recruit the LC and/or VTA neurons into the broad network underlying the new learning, through a Hebbian-like mechanism. Offline firing of these neuromodulatory neurons in time with replay of the "memory ensemble" during sleep would increase the probability and rate of firing of individual pyramidal cells by decreasing after hyperpolarization, thereby increasing excitability (McCormick and Prince, 1988). It is indeed well established that NE promotes LTP (Neuman and Harley, 1983), so if LC cells are firing in close temporal proximity to the replay ensemble, then the connections within that ensemble will be reinforced.

LC activity during SWS after learning

Several years ago, a series of pharmacological studies in the rat implicated the noradrenergic system in a late offline stage of memory consolidation ~1–2 h after learning (Tronel et al., 2004). Complementary studies showed an increase in release of NE in the same time window, after learning. These results encouraged us to look at activity of LC neurons during the hours after learning, when the rats spent most of the time sleeping. Recording unit activity from this tiny pontine nucleus (~1500 neurons in the rat), we found an increase in LC activity during SWS, 2 h after learning of the same odor discrimination task. This increase was seen only in rats that had learned the task. Interestingly, it was also seen after retrieval from remote memory, suggesting an LC involvement of reconsolidation of a reactivated memory trace (Eschenko and Sara, 2008).

SWS is characterized by high-amplitude, low-frequency oscillations (~1 Hz) called slow waves (hence SWS). During these oscillations, cortical neurons are hyperpolarized in the "down" state and fire action potentials in the "up" state. Examination of the temporal relation between LC action potentials and cortical oscillations reveals that LC neurons are phase-locked to the slow wave. LC neurons tend to fire on the rising phase during the transition from down to up state. Thus, unit firing of LC neurons precedes the synchronous firing of cortical neurons with almost no overlap (Eschenko et al., 2012). This observation corroborated an earlier study reporting that LC neurons and neurons of the frontal cortex fire in phasic opposition, when both regions are in an oscillating mode (Sara and Hervé-Minvielle, 1995). Release of NE in the forebrain by LC neurons firing immediately before the synchronous firing of cortical neurons would be the ideal situation for promoting synaptic plasticity within a reactivated network (Sara, 2015).

Slow waves, spindles, and ripples in memory consolidation

Slow waves play a crucial role in offline memory consolidation during sleep. Driving the sleeping brain with transcranial direct current stimulation to function in a slow oscillating mode during SWS (or "boosting the slow oscillations") facilitates memory in human subjects (Marshall et al., 2006, 2011). It has recently been discovered that mild acoustic stimulation is effective in increasing the magnitude of slow waves during sleep and that this en-

hancement leads to the same memory enhancement as the transcranial DC stimulation (Bellesi et al., 2014).

The depolarizing phase of the slow wave generates spindle oscillations at 12–15 Hz within the "up" state, via corticothalamic feedback loops (Steriade et al., 1993). In this way, spindles are nested within the slow oscillations (Mölle et al., 2002; Cox et al., 2014). A recent study confirmed the coupling of spindles with the slow oscillation and further showed that the timing of the spindles in relation to the slow oscillation was important for memory consolidation. Spindle peaks occurring during the transition from down to up state were predictive of subsequent improvement of performance of a word paired associate task (Niknazar et al., 2015). Earlier studies in humans showed an increase in spindle activity during sleep following learning (Gais et al., 2002; Mölle et al., 2004). We found a strikingly similar increase in spindles in rats after learning of an odor discrimination task, and this increase was positively correlated with subsequent improvement in memory performance (Eschenko et al., 2006).

Learning of semantically new words is followed by an increase in spindles in subsequent sleep, compared with spindle density during sleep following the learning of words that had some semantic relation to existing knowledge (Tamminen et al., 2013). Increase not only in density, but in spindle power, has been associated with improved memory performance (Rihm et al., 2014). Reexposure during SWS to an olfactory cue present during learning a visuospatial task increased power in the fast spindle range and improved retention the next day. The authors suggest that the learning-associated cue induced a high-frequency replay of ensemble activity in the hippocampus, which in turn drove the cortical spindle oscillations. Spontaneously occurring persistent offline environmental cues could be a mechanism by which a bias concerning which ensembles are replayed during sleep is introduced.

Finally, local spindles can be detected with intracerebral electrodes, and they are reported to be quite common, suggesting that sleep spindles can promote synaptic plasticity and memory consolidation in a "circuit-specific" manner (Nir et al., 2011).

The high-frequency ripple oscillation in the hippocampus is an intricate part of the two stage model. High-frequency firing of ensembles of neurons associated with the previous learning experience should promote the LTP underlying lasting memories. Indirect support for this essential role of high-frequency oscillation in the hippocampus comes from a few key experiments in rats. A learning-dependent increase in ripples during SWS was initially observed after a single session acquisition of an odor discrimination task. Rats that did not learn the task did not show this increase in ripples (Eschenko et al., 2008). A subsequent study, using a multisession spatial discrimination task, showed an increase in ripples during the sleep session immediately before behavioral expression of task mastery (Ramadan et al., 2009). Interruption of ripples by ripple-triggered electrical stimulation of the hippocampus prevented learning of that same spatial discrimination task (Ego-Stengel and Wilson, 2010; Girardeau et al., 2009). Because ensemble replay happens during the ripple, it is assumed that the increase of ripples after learning will include more replay. Interruption of the ripples will prevent the replay, thus accounting for the behavioral deficit.

Recent studies have confirmed in humans what was reported earlier in rats (Siapas and Wilson, 1998; Sirota et al., 2003 Mölle et al., 2006, 2009), that both spindles and hippocampal ripples are nested in slow oscillations. Staresina et al. (2015) used intracranial electrodes implanted in epileptic patients to study the temporal relation among slow oscillations, spindles, and ripples. Spindles were confined to the up state of the slow oscillation, and ripples tended to be clustered in the troughs of the spindles. An earlier fMRI study revealed increased hippocampal/neocortical connectivity during spindles (Andrade et al., 2011). These studies, together, provide evidence that temporally fine-tuned NREM sleep oscillatory activity provides ideal conditions for effective transfer of information from hippocampus to neocortex, an essential step in systems-level memory consolidation.

Clinical considerations

Disturbance of normal sleep–wake cycles and sleep stages is likely to contribute to cognitive deficits in several psychiatric disorders (Goerke et al., 2015). There is a large literature documenting sleep disturbances and their relation to memory function in schizophrenic patients. These disturbances include a reduction in the number of spindles (Göder et al., 2015; Manoach et al., 2016) and reduced coherence among spindles recorded from different cortical regions (Ferrarelli et al., 2007). Wamsley et al. (2012) found that schizophrenic patients did not show spontaneous improvement in performance of a motor sequence task after sleeping, as is seen in healthy controls. Moreover, there was a direct correlation in these patients, between the reduction in number and density of sleep spindles and the deficit in motor learning. This was taken by the authors as strong support for an essential role of sleep spindles in memory consolidation and opens new avenues of approach to treat cognitive deficits in schizophrenia.

A sequential hypothesis

Giuditta (1985) proposed early on a "sequential hypothesis" for SWS and REM sleep in memory processing, with each stage of sleep playing a distinct and complementary role. This was several years before there was any interest or experimental evidence for memory processing during SWS, and all eyes were focused on REM. The hypothesis was based on data from rats learning a very stressful multitrial avoidance task. Very large differences were observed in the structure of subsequent sleep, both SWS and REM, depending on whether the rats had learned or not. This led these investigators to propose, for the first time, that both stages of sleep participated in offline memory consolidation in a sequential manner. During SWS, "irrelevant" information is preprocessed and downgraded; during REM, "relevant" information is integrated into preexisting memories. There was no attempt to explain how information is "tagged" as relevant or not, and this question remains outstanding today. Giuditta's (1985) sequential hypothesis received little attention at the time, even though it was remarkably predictive of current views on the function of sleep. For example, "sleep processing is likely to result in the elimination of trivial or unusable information and the integration of useful information …with preexisting traces. The latter operation might involve the relocation of memory traces into different cerebral sites" (Ambrosini et al., 1988; for review, see Giuditta, 2014). Current theories of memory consolidation have emphasized this integration of new information with existing "schema" as an essential part of the process (Sara, 2000, 2010; Tse et al., 2007; Dudai et al., 2015). The notion of relocation of the memory trace to "different cerebral sites" is now widely accepted, with strong supporting evidence (Dudai et al., 2015 for review).

Recent support was added for the sequential view from a study in humans using a combined polygraphic, fMRI technique in an emotional learning task. SWS was found to be involved in the initial selection of information to be processed and REM sleep in the subsequent consolidation of the selected information (Cairney et al., 2015), much as Giuditta's (1985) model suggests.

Summary and perspectives

Contrary to the beliefs of the ancient Greeks, modern science has produced an impressive body of evidence documenting the essential role played by sleep states in offline memory consolidation. From the early, rather crude attempts to deprive rats of REM sleep by confining them on inverted flower pots in a pool of water, great progress has been made. Advances in computational capacities have facilitated analysis of multiple channels of EEG to provide new insights into the complex interaction of neocortical and hippocampal oscillatory activity, supporting the hypothesis of the essential role of dialogue between these two regions in offline memory consolidation. fMRI studies will continue to further our understanding of the dynamics of interplay among brain regions for systems-level consolidation. Multisite high-volume electrophysiological recordings permitted the discovery of ensemble replay during SWRs, especially during sleep.

Many other questions concerning the neurophysiological mechanisms underlying memory consolidation and the role of sleep, in particular, remain. For example, how are specific ensembles "tagged" for offline replay? Are these same memory ensembles actually reactivated again during retrieval of the memory (Dupret et al., 2010)? The specific roles of REM and NREM sleep remain elusive, although the evidence points to reactivation of neuronal activity during SWS and transcriptional storage during REM (Ribeiro et al., 1999). Advances in modern biotechnology are beginning to bring answers to these and other questions concerning the neurobiology of memory consolidation (e.g., Boyce et al., 2016). Meanwhile, unequivocal evidence points to the essential role of sleep states in these processes.

Response from Dual Perspective Companion Author–Gina Poe

Susan J. Sara provides a thorough review of research demonstrating that sleep is for memory consolidation and reconsolidation. The question remains: How? Sara's article has particular strength over many other reviews in that she pays particular attention to mechanism, highlighting rhythms, timing of reactivation, and neurochemical milieu. In the accompanying perspective, I parallel many of these lines, arguing with a different emphasis: that consolidation and reconsolidation of memories during sleep are the only time the normal brain can strategically erase components of memories to form a coherent schema. When new pieces of information are learned, synaptic weakening is an important part of reconsolidation. I argue that sleep, particularly sleep when the LC is silent (during spindle onset in the NREM transition to REM [TR] sleep phase and REM sleep), is the only time when synapses associated with inaccurate bits of information can be weakened, allowing that information to be forgotten. It is perhaps a stretch to say "forgetting" when referring to the targeted elimination of now incorrect bits of information, but I also discuss forgetting in terms of unwanted forgetting that would occur under circumstances when the LC is compromised during slow-wave sleep.

Sara's review clarifies a puzzle in sleep-for-memory research (is REM sleep for consolidation of procedural and emotional memories), showing how slow-wave sleep, rather than REM sleep, seems to be important for consolidating procedural memory. Her own research shows a key mechanism by which sleep serves to strengthen new learning while preserving old memories. But as argued in my accompanying article, additional waking practice could continue to strengthen synapses underlying learning, without need of sleep. In contrast, more waking practice cannot integrate new memories into old schema or erase irrelevant information during new learning. Studies in birds learning their song (Deregnaucourt et al., 2005) and imprinting (Jackson et al., 2008) and in humans learning to ride a reversed handlebar bicycle (Hoedlmoser et al., 2015), support the idea that targeted, careful pruning during REM sleep and NREM sleep spindles is necessary to remove noise that would otherwise crowd and obscure the memories we want to maintain.

A compelling question is how synapses encoding incorrect pieces of information, or those overpotentiated during prolonged activity of a sensory or motor circuit during wakefulness, as in Blake and Merzenich (2002) and Hanlon et al. (2009), are tagged for forgetting during sleep, while others are marked for strengthening. The finding that the density of sleep spindles correlated with worsened performance on the reverse handlebar bicycle (Hoedlmoser et al., 2015) is fascinating. Under what conditions would sleep serve to strengthen rather than erase that new oddball motor memory? If subjects knew they would have to ride with this reverse handlebar configuration for the rest of their lives, could they somehow tag that new circuit for retention and strengthening rather than elimination during sleep? In a question also asked at the end of Sara's article: how does the brain work to tag a new memory for retention while leaving others to be erased during sleep? Indeed, the opposite mechanism could serve: useless memories or interfering memory bits may be tagged for depotentiation, whereas those slated to be strengthened by sleep processes follow the usual consolidation course outlined in Sara's prospective. It is still early days in the collection of experimental evidence that sleep is for forgetting. Although indirect evidence abounds, direct evidence of the importance of depotentiation for memory and the exclusivity of depotentiation to LC-off periods is still needed.

References

Blake DT, Merzenich MM (2002) Effects of REM sleep on behaviorally induced changes in neuronal state: Neuronal replay during sleep? Seattle: Association of Professional Sleep Societies.

Deregnaucourt S, Mitra PP, Feher O, Pytte C, Tchernichovski O (2005) How sleep affects the developmental learning of bird song. Nature 433:710–716. CrossRef Medline

Hanlon EC, Faraguna U, Vyazovskiy VV, Tononi G, Cirelli C (2009) Effects of skilled training on sleep slow wave activity and cortical gene expression in the rat. Sleep 32:719–729. Medline

Hoedlmoser K, Birklbauer J, Schabus M, Eibenberger P, Rigler S, Mueller E (2015) The impact of diurnal sleep on the consolidation of a complex gross motor adaptation task. J Sleep Res 24:100–109. CrossRef Medline

Jackson C, McCabe BJ, Nicol AU, Grout AS, Brown MW, Horn G (2008) Dynamics of a memory trace: effects of sleep on consolidation. Curr Biol 18:393–400. CrossRef Medline

References

Ambrosini MV, Sadile AG, Gironi Carnevale UA, Mattiaccio M, Giuditta A (1988) The sequential hypothesis on sleep function: I. Evidence that the structure of sleep depends on the nature of the previous waking experience. Physiol Behav 43:325–337. CrossRef Medline

Andrade KC, Spoormaker VI, Dresler M, Wehrle R, Holsboer F, Sämann PG, Czisch M (2011) Sleep spindles and hippocampal functional connectivity in human NREM sleep. J Neurosci 31:10331–10339. CrossRef Medline

Aserinsky E, Kleitman N (1953) Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. Science 118:273–274. CrossRef Medline

Atherton LA, Dupret D, Mellor JR (2015) Memory trace replay: the shaping of memory consolidation by neuromodulation. Trends Neurosci 38:560–570. CrossRef Medline

Barnes DC, Wilson DA (2014) Slow-wave sleep-imposed replay modulates both strength and precision of memory. J Neurosci 34:5134–5142. CrossRef Medline

Bellesi M, Riedner BA, Garcia-Molina GN, Cirelli C, Tononi G (2014) Enhancement of sleep slow waves: underlying mechanisms and practical consequences. Front Syst Neurosci 8:208. CrossRef Medline

Bendor D, Wilson MA (2012) Biasing the content of hippocampal replay during sleep. Nat Neurosci 15:1439–1444. CrossRef Medline

Bouret S, Sara SJ (2004) Reward expectation, orientation of attention and locus coeruleus-medial frontal cortex interplay during learning. Eur J Neurosci 20:791–802. CrossRef Medline

Boyce R, Glasgow SD, Williams S, Adamantidis A (2016) Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. Science 352:812–816. CrossRef Medline

Buzsáki G (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 31:551–570. CrossRef Medline

Buzsáki G (1998) Memory consolidation during sleep: a neurophysiological perspective. J Sleep Res 7 [Suppl 1]:17–23. CrossRef Medline

Cairney SA, Ashton JE, Roshchupkina AA, Sobczak JM (2015) A dual role for sleep spindles in sleep-dependent memory consolidation? J Neurosci 35:12328–12330. CrossRef Medline

Calais JB, Ojopi EB, Morya E, Sameshima K, Ribeiro S (2015) Experience-dependent upregulation of multiple plasticity factors in the hippocampus during early REM sleep. Neurobiol Learn Mem 122:19–27. CrossRef Medline

Clemens Z, Fabó D, Halász P (2006) Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. Neurosci Lett 403:52–56. CrossRef Medline

Cox R, van Driel J, de Boer M, Talamini LM (2014) Slow oscillations during sleep coordinate interregional communication in cortical networks. J Neurosci 34:16890–16901. CrossRef Medline

Creery JD, Oudiette D, Antony JW, Paller KA (2015) Targeted memory reactivation during sleep depends on prior learning. Sleep 38:755–763. CrossRef Medline

Crick F, Mitchison G (1983) The function of dream sleep. Nature 304:111–114. CrossRef Medline

Dudai Y, Karni A, Born J (2015) The consolidation and transformation of memory. Neuron 88:20–32. CrossRef Medline

Dupret D, O'Neill J, Pleydell-Bouverie B, Csicsvari J (2010) The reorganization and reactivation of hippocampal maps predict spatial memory performance. Nat Neurosci 13:995–1002. CrossRef Medline

Ego-Stengel V, Wilson MA (2010) Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. Hippocampus 20:1–10. CrossRef Medline

Eschenko O, Sara SJ (2008) Learning-dependent, transient increase of activity in noradrenergic neurons of locus coeruleus during slow wave sleep in the rat: brain stem-cortex interplay for memory consolidation? Cereb Cortex 18:2596–2603. CrossRef Medline

Eschenko O, Mölle M, Born J, Sara SJ (2006) Elevated sleep spindle density after learning or after retrieval in rats. J Neurosci 26:12914–12920. CrossRef Medline

Eschenko O, Ramadan W, Mölle M, Born J, Sara SJ (2008) Sustained increase in hippocampal sharp-wave ripple activity during slow-wave sleep after learning. Learn Mem 15:222–228. CrossRef Medline

Eschenko O, Magri C, Panzeri S, Sara SJ (2012) Noradrenergic neurons of the locus coeruleus are phase locked to cortical up-down states during sleep. Cereb Cortex 22:426–435. CrossRef Medline

Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, Watson A, Bria P, Tononi G (2007) Reduced sleep spindle activity in schizophrenia patients. J Psychiatry 164:483–492. CrossRef Medline

Fishbein W (1971) Disruptive effects of rapid eye movement sleep deprivation on long-term memory. Physiol Behav 6:279–282. CrossRef Medline

Fishbein W, Gutwein BM (1977) Paradoxical sleep and memory storage processes. Behav Biol 19:425–464. CrossRef Medline

Fogel SM, Ray LB, Binnie L, Owen AM (2015) How to become an expert: a new perspective on the role of sleep in the mastery of procedural skills. Neurobiol Learn Mem 125:236–248. CrossRef Medline

Gais S, Mölle M, Helms K, Born J (2002) Learning-dependent increases in sleep spindle density. J Neurosci 22:6830–6834. Medline

Genzel L, Dresler M, Wehrle R, Grözinger M, Steiger A (2009) Slow wave sleep and REM sleep awakenings do not affect sleep dependent memory consolidation. Sleep 32:302–310. Medline

Gilson M, Deliens G, Leproult R, Bodart A, Nonclercq A, Ercek R, Peigneux P (2015) REM-enriched naps are associated with memory consolidation for sad stories and enhance mood-related reactivity. Brain Sci 6:piiE1. CrossRef Medline

Girardeau G, Benchenane K, Wiener SI, Buzsáki G, Zugaro MB (2009) Selective suppression of hippocampal ripples impairs spatial memory. Nat Neurosci 12:1222–1223. CrossRef Medline

Giuditta A (1985) A sequential hypothesis for the function sleep. In: Sleep 1984 (Koella WP, Ruther E, Schulz H, eds), pp 222–224. Stuttgart: Fischer Verlag.

Giuditta A (2014) Sleep memory processing: the sequential hypothesis. Front Syst Neurosci 8:219. CrossRef Medline

Göder R, Graf A, Ballhausen F, Weinhold S, Baier PC, Junghanns K, Prehn-Kristensen A (2015) Impairment of sleep-related memory consolidation in schizophrenia: relevance of sleep spindles? Sleep Med 16:564–569. CrossRef Medline

Goerke M, Muller NG, Cohrs S (2015) Sleep-dependent memory consolidation and its implications for psychiatry. J Neural Transm (Vienna). Advance online publication. Retrieved Oct. 30, 2015. doi: 10.1007/s00702–015-1476–3. CrossRef Medline

Groch S, McMakin D, Guggenbühl P, Rasch B, Huber R, Wilhelm I (2016) Memory cueing during sleep modifies the interpretation of ambiguous scenes in adolescents and adults. Dev Cogn Neurosci 17:10–18. CrossRef Medline

Hars B, Hennevin E (1987) Impairment of learning by cueing during postlearning slow-wave sleep in rats. Neurosci Lett 79:290–294. CrossRef Medline

Hars B, Hennevin E, Pasques P (1985) Improvement of learning by cueing during postlearning paradoxical sleep. Behav Brain Res 18:241–250. CrossRef Medline

Hennevin E, Leconte P (1971) [The function of paradoxical sleep: facts and theories]. Annee Psychol 71:489–519. CrossRef Medline

Horne JA, McGrath MJ (1984) The consolidation hypothesis for REM sleep function: stress and other confounding factors—a review. Biol Psychol 18:165–184. CrossRef Medline

Hutchison IC, Rathore S (2015) The role of REM sleep theta activity in emotional memory. Front Psychol 6:1439. CrossRef Medline

Jenkins J, Dallenbach K (1924) Obliviscence during sleep and waking. J Psychol 35:605–612. CrossRef

Jouvet M, Michel F (1960) [New research on the structures responsible for the "paradoxical phase" of sleep]. J Physiol (Paris) 52:130–131. Medline

Kudrimoti HS, Barnes CA, McNaughton BL (1999) Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. J Neurosci 19:4090–4101. Medline

Leconte P, Bloch V (1970a) [Effect of paradoxical sleep deprivation on the acquisition and retention of conditioning in rats]. J Physiol (Paris) 62 [Suppl 2]:290.

Leconte P, Bloch V (1970b) [Deficiency in retention of conditioning after deprivation of paradoxical sleep in rats]. C R Acad Sci Hebd Seances Acad Sci D 271:226–229. Medline

Llewellyn S, Hobson JA (2015) Not only. but also: REM sleep creates and NREM Stage 2 instantiates landmark junctions in cortical memory networks. Neurobiol Learn Mem 122:69–87. CrossRef Medline

Manoach DS, Pan JQ, Purcell SM, Stickgold R (2016) Reduced sleep spindles in schizophrenia: a treatable endophenotype that links risk genes to impaired cognition? Biol Psychiatry 80:599–608. CrossRef Medline

Marshall L, Helgadóttir H, Mölle M, Born J (2006) Boosting slow oscilla-

tions during sleep potentiates memory. Nature 444:610–613. CrossRef Medline
Marshall L, Kirov R, Brade J, Mölle M, Born J (2011) Transcranial electrical currents to probe EEG brain rhythms and memory consolidation during sleep in humans. PLoS One 6:e16905. CrossRef Medline
McCormick DA, Prince DA (1988) Noradrenergic modulation of firing pattern in guinea pig and cat thalamic neurons, in vitro. J Neurophysiol 59:978–996. Medline
Miller CH (1975) Dreams and dreaming: the current state of the art. Am J Psychoanal 35:135–146. CrossRef Medline
Mölle M, Marshall L, Gais S, Born J (2002) Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. J Neurosci 22:10941–10947. Medline
Mölle M, Marshall L, Gais S, Born J (2004) Learning increases human electroencephalographic coherence during subsequent slow sleep oscillations. Proc Natl Acad Sci U S A 101:13963–13968. CrossRef Medline
Mölle M, Yeshenko O, Marshall L, Sara SJ, Born J (2006) Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. J Neurophysiol 96:62–70. CrossRef Medline
Mölle M, Eschenko O, Gais S, Sara SJ, Born J (2009) The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. Eur J Neurosci 29:1071–1081. CrossRef Medline
Neuman RS, Harley CW (1983) Long-lasting potentiation of the dentate gyrus population spike by norepinephrine. Brain Res 273:162–165. CrossRef Medline
Niknazar M, Krishnan GP, Bazhenov M, Mednick SC (2015) Coupling of thalamocortical sleep oscillations are important for memory consolidation in humans. PLoS One 10:e0144720. CrossRef Medline
Nir Y, Staba RJ, Andrillon T, Vyazovskiy VV, Cirelli C, Fried I, Tononi G (2011) Regional slow waves and spindles in human sleep. Neuron 70:153–169. CrossRef Medline
Pearlman CA (1969) Effect of rapid eye movement (dreaming) sleep deprivation on retention of avoidance learning in rats. Rep No 563. Rep US Naval Submar Med Cent 22:1–4. Medline
Plihal W, Born J (1997) Effects of early and late nocturnal sleep on declarative and procedural memory. J Cogn Neurosci 9:534–547. CrossRef Medline
Ramadan W, Eschenko O, Sara SJ (2009) Hippocampal sharp wave/ripples during sleep for consolidation of associative memory. PLoS One 4:e6697. CrossRef Medline
Rasch B, Born J (2013) About sleep's role in memory. Physiol Rev 93:681–766. CrossRef Medline
Rasch B, Büchel C, Gais S, Born J (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 315:1426–1429. CrossRef Medline
Ravassard P, Hamieh AM, Joseph MA, Fraize N, Libourel PA, Lebarillier L, Arthaud S, Meissirel C, Touret M, Malleret G, Salin PA (2015) REM sleep-dependent bidirectional regulation of hippocampal-based emotional memory and LTP. Cereb Cortex 26:1488–1500. CrossRef Medline
Ribeiro S, Goyal V, Mello CV, Pavlides C (1999) Brain gene expression during REM sleep depends on prior waking experience. Learn Mem 6:500–508. CrossRef Medline
Ribeiro S, Mello CV, Velho T, Gardner TJ, Jarvis ED, Pavlides C (2002) Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. J Neurosci 22:10914–10923. Medline
Rihm JS, Diekelmann S, Born J, Rasch B (2014) Reactivating memories during sleep by odors: odor specificity and associated changes in sleep oscillations. J Cogn Neurosci 26:1806–1818. CrossRef Medline
Sara SJ (2000) Strengthening the shaky trace through retrieval. Nat Rev Neurosci 1:212–213. CrossRef Medline
Sara SJ (2010) Reactivation, retrieval, replay and reconsolidation in and out of sleep: connecting the dots. Front Behav Neurosci 4:185. CrossRef Medline
Sara SJ (2015) Locus coeruleus in time with the making of memories. Curr Opin Neurobiol 35:87–94. CrossRef Medline
Sara SJ, Hervé-Minvielle A (1995) Inhibitory influence of frontal cortex on locus coeruleus neurons. Proc Natl Acad Sci U S A 92:6032–6036. CrossRef Medline
Sara SJ, Segal M (1991) Plasticity of sensory responses of locus coeruleus neurons in the behaving rat: implications for cognition. Prog Brain Res 88:571–585. CrossRef Medline
Saxvig IW, Lundervold AJ, Grønli J, Ursin R, Bjorvatn B, Portas CM (2008) The effect of a REM sleep deprivation procedure on different aspects of memory function in humans. Psychophysiology 45:309–317. CrossRef Medline
Schultz W (2001) Reward signaling by dopamine neurons. Neuroscientist 7:293–302. CrossRef Medline
Siapas AG, Wilson MA (1998) Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. Neuron 21:1123–1128. CrossRef Medline
Siegel JM (2001) The REM sleep-memory consolidation hypothesis. Science 294:1058–1063. CrossRef Medline
Singer AC, Frank LM (2009) Rewarded outcomes enhance reactivation of experience in the hippocampus. Neuron 64:910–921. CrossRef Medline
Sirota A, Csicsvari J, Buhl D, Buzsáki G (2003) Communication between neocortex and hippocampus during sleep in rodents. Proc Natl Acad Sci U S A 100:2065–2069. CrossRef Medline
Skaggs WE, McNaughton BL (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. Science 271:1870–1873. CrossRef Medline
Smith C (1985) Sleep states and learning: a review of the animal literature. Neurosci Biobehav Rev 9:157–168. CrossRef Medline
Smith C (2001) Sleep states and memory processes in humans: procedural versus declarative memory systems. Sleep Med Rev 5:491–506. CrossRef Medline
Smith C, Kitahama K, Valatx JL, Jouvet M (1974) Increased paradoxical sleep in mice during acquisition of a shock avoidance task. Brain Res 77:221–230. CrossRef Medline
Sprague RK (1977) Aristotle and the metaphysics of sleep. Rev Metaphysics 31:230–241.
Staresina BP, Bergmann TO, Bonnefond M, van der Meij R, Jensen O, Deuker L, Elger CE, Axmacher N, Fell J (2015) Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. Nat Neurosci 18:1679–1686. CrossRef Medline
Steriade M, Contreras D, Curró Dossi R, Nunez A (1993) The slow (<1 Hz) oscillation in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation in interacting thalamic and neocortical networks. J Neurosci 13:3284–3299. Medline
Tamminen J, Lambon Ralph MA, Lewis PA (2013) The role of sleep spindles and slow-wave activity in integrating new information in semantic memory. J Neurosci 33:15376–15381. CrossRef Medline
Tronel S, Feenstra MG, Sara SJ (2004) Noradrenergic action in prefrontal cortex in the late stage of memory consolidation. Learn Mem 11:453–458. CrossRef Medline
Tse D, Langston RF, Kakeyama M, Bethus I, Spooner PA, Wood ER, Witter MP, Morris RG (2007) Schemas and memory consolidation. Science 316:76–82. CrossRef Medline
Vertes RP, Eastman KE (2000) The case against memory consolidation in REM sleep. Behav Brain Sci 23:867–876; discussion 904–1121.
Vogel GW (1975) A review of REM sleep deprivation. Arch Gen Psychiatry 32:749–761. CrossRef Medline
Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R (2002) Practice with sleep makes perfect: sleep-dependent motor skill learning. Neuron 35:205–211. CrossRef Medline
Wamsley EJ, Tucker MA, Shinn AK, Ono KE, McKinley SK, Ely AV, Goff DC, Stickgold R, Manoach DS (2012) Reduced sleep spindles and spindle coherence in schizophrenia: mechanisms of impaired memory consolidation? Biol Psychiatry 71:154–161. CrossRef Medline
Wiesner CD, Pulst J, Krause F, Elsner M, Baving L, Pedersen A, Prehn-Kristensen A, Göder R (2015) The effect of selective REM-sleep deprivation on the consolidation and affective evaluation of emotional memories. Neurobiol Learn Mem 122:131–141. CrossRef Medline
Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. Science 265:676–679. CrossRef Medline