Contributions of Post-learning REM and NREM Sleep to Memory Retrieval

Kevin J. MacDonald & Kimberly A. Cote

Brock University

This document is the unformatted accepted manuscript of the article published by *Sleep Medicine Reviews* and available at https://doi.org/10.1016/j.smrv.2021.101453.

Corresponding author:
Kimberly Cote, PhD
Psychology Department
Brock University
1812 Sir Isaac Brock Way
St. Catharines, Ontario,
L2S 3A1
CANADA
Email: kcote@brocku.ca

Acknowledgements:

The Brock University Sleep Research Laboratory is funded by the Natural Sciences and Engineering Research Council (NSERC) of Canada

Summary

It has become clear that sleep after learning has beneficial effects on the later retrieval of newly acquired memories. The neural mechanisms underlying these effects are becoming increasingly clear as well, particularly those of non-REM sleep. However, much is still unknown about the sleep and memory relationship: the sleep state or features of sleep physiology that associate with memory performance often vary by task or experimental design, and the nature of this variability is not entirely clear. This paper describes pertinent features of sleep physiology and provides a detailed review of the scientific literature indicating beneficial effects of post-learning sleep on memory retrieval. This paper additionally introduces a hypothesis which attributes these beneficial effects of post-learning sleep to separable processes of memory reinforcement and memory refinement whereby reinforcement supports one's ability to retrieve a given memory and refinement supports the precision of that memory retrieval in the context of competitive alternatives. It is observed that features of non-REM sleep are involved in a post-learning substantiation of memory representations that benefit memory performance; thus, memory reinforcement is primarily attributed to non-REM sleep. Memory refinement is primarily attributed to REM sleep given evidence of bidirectional synaptic plasticity in REM sleep and findings from studies of selective REM sleep deprivation.

***Keywords*:** Sleep, memory, memory retrieval, REM sleep, non-REM sleep, memory consolidation

Abbreviations

EEG	electroencephalography
PGO	ponto-geniculo-occipital
LTP	long-term potentiation
NREM	non-REM
SR2	sleep reinforcement and refinement

Glossary of terms

Declarative memory	Memory for past events and facts
Half-night paradigm	Experimental paradigm in which the effects of early-night sleep relatively rich in slow wave sleep are compared to the effects of late-night sleep relatively rich in REM sleep.
Hippocampal theta rhythm	Neural oscillation of 5–8 Hz observed in the hippocampus of rats during active exploration and REM sleep
Long-term depression	Relatively long-lasting decrease in synaptic strength resulting from synaptic activity
Long-term potentiation	Relatively long-lasting increase in synaptic strength resulting from synaptic activity and consisting an early and late stage
Memory consolidation	Process through which memories are transformed from an initial labile state to a more stable and longer lasting state integrated with existing memories.
Memory reactivation	Reoccurrence during sleep of specific patterns of neural activity that were present during learning
Memory representation	The neural changes underlying a memory; also referred to as a memory trace or engram.
Procedural memory	Memory for acquired skills and habits
P waves	Biphasic field potential generated in the pons and present during REM sleep; also termed ponto-geniculo-occipital waves when the lateral geniculate nucleus and occipital cortex are involved
Sharp wave ripples	Composite neural events in the hippocampus consisting of a large deflection (sharp wave) followed by high-frequency oscillations (ripple)
Slow waves	Term for 0.5–4 Hz activity that is present in N2 NREM sleep and dominates N3 NREM sleep; includes both surface slow oscillations (<1 Hz) and delta waves (1–4 Hz).
Spindle	Burst-like sequences of 10–16 Hz sinusoidal activity appearing in EEG during N2 and N3 NREM sleep

1

Memory performance benefits from sleep relative to wake have been observed across many paradigms and memory tasks. For example, sleep improves cued recall of word pairs [1,2] and promotes performance gains in newly learned skills [3,4]. Sleep may even promote forgetting of some superfluous memories and associations [5,6]. The complexity of the sleep–memory relationship may in part be attributed to the multifaceted nature of sleep physiology. This review outlines sleep physiology and existing hypotheses regarding sleep and memory before introducing a new hypothesis concerning the effect of sleep states on memory performance. Following these introductions, the literature connecting sleep to memory retrieval is discussed.

Sleep Physiology

In humans, sleep is composed of stages marked by patterns of brain activity, eye movements, and muscle tone, measured via electroencephalography (EEG), electrooculography, and electromyography, respectively. Rapid eye movement (REM) sleep, scored as stage R, is distinct from multiple stages of non-rapid eye movement (NREM) sleep scored as stages N1, N2, and N3 [7]. In healthy adult sleep, these stages appear in a predictable and cyclical pattern [8,9]. A typical night of sleep starts with a brief period of stage N1 sleep and progresses into this cycle with deeper NREM stages of N2 and then N3 followed by a brief period of REM sleep before returning to NREM sleep to complete the roughly 90-min cycle. Brief returns to wakefulness and stage N1 notwithstanding, this cycle continues throughout the night although the relative durations of N2, N3, and REM sleep within the cycle change over the night. In the first half of the night (i.e., the first 2–3 cycles), there is a relative abundance of N3 sleep over REM sleep. In the second half of the night, there is more REM sleep and N3 sleep may not be observed at all. N2 sleep is present throughout the night and constitutes roughly 50% of sleep duration.

The major patterns of neural activity that define NREM sleep are spindles and slow waves. Spindles are burst-like sequences of approximately 10–16 Hz sinusoidal activity appearing in surface EEG and generated by neuronal oscillations in the thalamus of sleeping mammals [10,11]. Within individual humans, there are slow (≈10 Hz) and fast (≈13 Hz) spindles; however, there considerable individual differences in the frequency of slow and fast spindles [10,12]. The functions of spindles, fast or slow, are not certain, but fast spindles have been frequently linked to memory processing [13–17]. Slow wave activity in surface EEG is a definitive factor in N3 sleep, or slow wave sleep, and consists of 0.5–4 Hz activity, often divided as surface slow oscillations (<1 Hz) and delta waves (1–4 Hz) [11]. Slow waves in surface EEG reflect the oscillation of populations of cortical neurons between an "up" state of cellular membrane depolarizing and neuronal firing and a largely silent "down" state of cellular membrane hyperpolarization with both intracortical and thalamocortical circuits mediating the patterns of this oscillation [18]. Notably, the amount of slow wave activity appears to be determined in a local, use-dependent manner such that, for example, immobilization of an arm during the day reduces slow wave activity observed in the contralateral sensorimotor cortex [19]. NREM sleep in mammals also includes sharp wave ripples, which occur in the CA1 region of the hippocampus and consist of a large 40–100 ms deflection followed by fast oscillations [20]. Structurally similar events occur in other brain regions, including sharp waves and ripples in the olfactory cortex and amygdala and the neocortical K-complex with spindle [20]. Of importance to sleep and memory, hippocampal ripples have been identified as a source of memory replay during NREM sleep as both neocortical and hippocampal neuron firing patterns surrounding these events resemble a temporally compressed version of the patterns observed in recent learning in rats [21–23]. Critically, disrupting hippocampal replay has been shown to lead to

memory deficits, specifically for memories corresponding to neuronal ensembles targeted by the disruption procedure [24]. The timing of sharp wave ripples, memory reactivations, slow waves, and spindles are highly linked and appear to be coordinated by the up and down states of intracortical slow oscillations as part of a hippocampal-thalamic-neocortical circuit [25–29].

REM sleep electrophysiology includes theta activity and biphasic potentials termed ponto-geniculo-occipital (PGO) waves (P waves when only the pontine element is identified), although both features are more evident and well studied in rodents than in humans. The hippocampal theta rhythm is a neural oscillation generated in the brainstem that is observed during active exploration, prominent during REM sleep, and implicated in learning and memory [30–32]. Coherent theta activity has been observed in the rat amygdala and prefrontal cortex [33–35]. The hippocampal theta rhythm in small mammals such as rats has a 5–8 Hz frequency, but, in humans, there is evidence for a ≈3 Hz analog [36–38]. PGO waves are waveforms generated in the pons that propagate through the lateral geniculate nucleus of the thalamus and potentially to multiple cortical regions; they have been identified in REM sleep of mammals, including cats, rats, and non-human primates, but, due to ethical and practical barriers associated with the required invasive recordings, there is only limited and suggestive evidence of similar P in humans[39–43]. In rats, P waves are typically phase-locked with the hippocampal theta rhythm [44,45]. Both PGO waves and the hippocampal theta rhythm have been implicated in synaptic change. Blocking PGO waves in kittens impairs developmentally beneficial reductions in plasticity of the lateral geniculate nucleus [46]. In the rat hippocampus, the effect of hippocampal cell stimulation on synaptic strength is bidirectionally modulated by the phase of the theta rhythm, increasing strength when stimulation occurs during peaks and decreasing strength when it occurs during troughs [47–49].

Hypotheses of Sleep and Memory

Concepts of Memory

Memory function consists of the encoding of events into neural representations, or engrams, to create memory traces that can be subsequently expressed as thoughts or behaviours through the process of memory retrieval. Hypotheses of sleep and memory often address how sleep contributes to memory consolidation, the process by which a memory is transformed from a labile, temporary state into a more stable, long-lasting state that is integrated with existing memories [50]. Hypotheses of sleep and memory have also valued distinctions between memory systems; the declarative memory system includes episodic memory, referring to memories that are autobiographical and linked to a temporal or spatial context, and semantic memory, referring to general knowledge, whereas non-declarative memory systems include, among others, procedural memories for acquired skills and habits [51].

Memory retrieval is assumed to involve the reactivation of encoded memory traces via internal or external cues; thus, the retrievability of a memory depends on both the integrity of the engram (i.e., its “availability”) and its accessibility via cue [52,53]. Of course, memory traces do not exist in isolation. Interference refers to situations in which retrieval of a given memory is impaired by the presence of one or more additional representations that may be associated with the same retrieval cues [54]. Interference can result in a failure of retrieval or, when the quality of retrieval is measured on a continuous scale, reduced fidelity of memory retrieval. An emphasis on the fidelity or precision of retrieval is prominent in research on visual working memory, and a role for interference in retrieval precision has been explained [55]. Memory retrieval may take various forms depending on the task (cued recall, free recall, recognition, or the execution of movements), or, within recognition memory, whether contextual information from the learning

event also retrieved, termed recollection, or not retrieved, termed familiarity.

Memories are thought to be acquired through long-term potentiation (LTP) and long-term depression, which respectively refer to long-lasting increases and decreases in synaptic strength typically induced by stimulation [56,57]. LTP consists of an early stage independent of protein synthesis and a late stage requiring protein synthesis. Long-term depression can involve protein synthesis and can occur de novo or after LTP, in which case it is referred to as depotentiation. The formation and alteration of dendritic spines are thought to be important in the experience-dependent synaptic plasticity underlying learning and memory [58]. The density and size of dendritic spines and hence the number of synapses and synaptic strength generally increase with LTP and decrease with long-term depression [58].

Existing Hypotheses

One approach to understanding the role of sleep in memory has been to associate different sleep states to different types of memory in variations of a “dual process” hypothesis. Investigation of dissociable NREM and REM sleep effects has included use of the half-night paradigm in which researchers compare the effects of an early-night sleep retention period naturally rich in deep NREM sleep to the effects of a late-night sleep retention period naturally rich in REM sleep. To this end, researchers have also used selective deprivation of REM sleep both in rodents—by placing subjects in an apparatus in which REM sleep onset muscle atonia causes awakenings after falling into water—and in humans—by waking participants upon polysomnographic signs of REM sleep. Although details varied by account and evidence considered, the emergent notion from research with these paradigms was that new declarative memories preferentially benefit from NREM sleep, typically slow wave sleep, and new non-declarative, especially procedural, memories preferentially benefit from REM sleep [59–62].

However, a dissociation of NREM and REM sleep serving different memory systems is incongruent with many findings. For example, simple procedural memory tasks were seen to be more dependent on stage 2 NREM sleep than REM sleep [63,64]. Conversely, REM sleep was implicated in memory for prose [65,66] and learning a second language [67]. It may be that both sleep states support declarative and procedural memory, and REM sleep has specific benefits for new memories in "complex" tasks, although the defining features of a complex task are undetermined [64,68]. Genzel et al. [69] argued that REM sleep supports emotional or "amygdala-related" memory processing whereas NREM sleep is important for cortically based memories. Indeed, REM sleep has been implicated in emotionally charged memory while REM sleep connections with other material is less conclusive [69,70], but this hypothesis has received little direct testing.

Considering the sequential nature of sleep cycles led to the development of the sequential hypothesis which emphasizes the importance of slow wave sleep to REM sleep sequences in memory processing. The sequential hypothesis proposes that NREM sleep contains selective processes that weaken non-adaptive memories before REM sleep stores the surviving memories and integrates them with preexisting memories [71,72]. This hypothesis is supported by studies relating overnight retention of words to the integrity of NREM-REM sleep cycles [73,74]. There is evidence for adaptive selectivity in memory processing over sleep and for sleep involvement in the integration of new memories with existing knowledge [75]; however, it is inconclusive whether NREM sleep and REM sleep provide these benefits specifically and respectively.

The active systems consolidation hypothesis similarly proposes that NREM and REM sleep work together in memory processing, and it is especially focused on the neural mechanisms mediating sleep-dependent memory processing [76,77]. This hypothesis states that events of

wake are encoded across cortical networks and bound together by the medial temporal lobe; then, during slow wave sleep, neuronal replay originating from the hippocampus consolidates memory via hippocampal-neocortical information transfer and the strengthening of cortico-cortical connections. NREM sleep features, including slow waves, spindles, and ripples, are thought to facilitate the required reactivation of neuronal ensembles. REM sleep is thought to subsequently stabilize changes acquired in NREM sleep. The active systems consolidation hypothesis is supported by many findings, including memory benefits from externally-induced reactivations during NREM sleep [e.g., 78], reported evidence of hippocampal-to-neocortical information transfer via precise triple-coupling of slow oscillations, spindles, and ripples [79], and increased expression of genes associated with synaptic plasticity in the cortex during REM sleep [80]. An alternative contextual binding model of episodic memory attributes benefits of sleep for memory not to hippocampal-neocortical information transfer but to a relative absence of contextual interference that otherwise is incurred during wakefulness and impairs memory performance [81]. This proposal is backed, in part, by evidence that sleep preferentially benefits forms of associative memory [1,82–84].

Alternative distinctions for the roles of NREM and REM sleep have also been proposed. Poe et al. [85] proposed that NREM sleep slow wave activity is important for converting early LTP into long-lasting LTP, in part because late LTP requires protein synthesis [86,87] which is increased during slow wave sleep [88,89]. Poe et al. [85] proposed that REM sleep is an opportune time for bidirectional synaptic change given that relatively high cholinergic activity [90] favours induction of LTP [91] and that low norepinephrinergic activity [92] is essential for depotentiation [93,94]. Theta activity of REM sleep has been proposed as a potential vehicle for selective strengthening and weakening of memories [95]. This proposal is founded on the

previously noted phase-dependent bidirectional synaptic plasticity associated with the hippocampal theta rhythm in rats [47–49] and evidence that rat hippocampal neurons activity during exploration fired on theta rhythm peaks during post-exploration REM sleep and then on theta rhythm troughs after the explored setting became familiar [95]. Seibt and Frank [96] proposed a similar model. They propose that REM sleep selectively strengthens and weakens memory traces marked for these actions by NREM sleep through memory reactivation and oscillatory activity within circuits primed for such action through transient neuronal changes induced by waking experience.

Synaptic weakening, long-term depotentiation, or forgetting during sleep has been considered important in preventing the saturation of memory systems and increasing energy demands that would result from unchecked learning of patterns and associations during wake. Crick and Mitchison [5] proposed that REM sleep served to eliminate the unwanted memories or "parasitic modes" that would result from continuous modifications by experience. Giuditta [97] similarly proposed that sleep preserved adaptive memories while trimming them of irrelevant or competing traces, but attributed the weakening of the non-adaptive traces to slow wave sleep. The influential synaptic homeostasis hypothesis [98] argues that system saturation is prevented by an activity-dependent down-selection process largely associated with the oscillating up and down states of cortical neurons during NREM sleep. This process is proposed to benefit memory performance by increasing signal-to-noise ratios. Poe [6] expanded upon her earlier model that REM sleep is an opportune time for bidirectional synaptic change, proposing that targeted depotentiation of synapses during sleep would contribute to forgetting, a reduction of noise in perceptual and memory systems, schema development, and synaptic pruning during development. Poe [6] proposed that the inactivity of norepinephrine-providing locus coeruleus

neurons during REM sleep and during the second preceding spindles [92] makes these two periods ideal for the targeted forgetting of somatosensory and hippocampal memories. Poe [6] further proposed that reduced extracellular dopamine during slow wave sleep [99] provides a similar opportunity for the targeted forgetting of dorsal striatal-dependent memories, including motor and procedural memories.

Hypotheses proposing complementary functions for NREM and REM sleep are supported by a few studies showing that improvements in visual texture discrimination, a learned perceptual skill, are best promoted by sleep containing both slow wave sleep and REM sleep [100–102]. However, studies of sleep and memory often implicate either NREM sleep or REM sleep and rarely both for the same memory task. Identification of a precise role for REM sleep in memory processing has been particularly elusive [70], and it remains undetermined whether sleep promotes active and selective forgetting. Multiple existing models account for research into memory processing during sleep; however, plenty of questions remain regarding the effects of sleep on memory performance, such as in what situations and with what measures will memory performance associate with properties of NREM sleep, in what situations and with what measures will measures of performance associate with properties of REM sleep, and what specific effect on memory performance is granted by each of these sleep states?

Sleep Reinforcement and Refinement Hypothesis

Here a new hypothesis is presented in which sleep is proposed to support later retrieval of newly acquired memories through reinforcement and refinement. In this sleep reinforcement and refinement (SR2) hypothesis[1], memory reinforcement is primarily attributed to NREM sleep, and memory refinement is primarily attributed to REM sleep. NREM sleep memory reinforcement is

[1] The SR2 hypothesis was formulated by K. MacDonald through his doctoral dissertation.

proposed to maintain or potentially increase the retrievability of memories by supporting both the integrity of the engram and its links to retrieval cues. REM sleep memory refinement is proposed to support the precision of memory retrieval through selective preservation of dominant memory traces and weakening of competing memory traces that may impair the quality and reliability of memory retrieval. In this context, a dominant memory trace is the one which corresponds to the memory that is most likely to be retrieved in a given context, whereas competing memory traces are those which share internal or external retrieval cues to the dominant trace and may alternatively be retrieved. Such dominance may be indicated by synaptic strength. NREM and REM sleep are considered primary for reinforcement and refinement, respectively; however, it is acknowledged that a perfect dissociation is unlikely and that features of sleep physiology characteristic of a specific sleep state but not exclusive to it may also contribute to reinforcement and refinement in ways beyond this proposed dissociation (e.g., a reduction in norepinephrine also linked to spindles [92]). Reinforcement and refinement offer separable contributions to retrieval, and their effects are considered compatible and synergistic such that the greatest benefit to retrieval is assumed to result from alternating periods of reinforcement followed by refinement as would occur in a typical sleep cycle. General reinforcement without subsequent refinement may benefit retrievability but impair the precision of memory retrieval because both dominant and any competing memory representations are reinforced. A depiction of the effects of learning, reinforcement, and refinement on the formation and processing of memories is provided in Figure 1.

This hypothesis may be expressed using terms of signal detection theory. It is assumed that a dominant memory trace (signal) exists within noise from highly related and competing memory traces (interference) and from random or external sources. It is proposed that NREM

sleep reinforces memories by further raising signal and interference levels above random and external noise. This effect may occur through application of gain to new memory traces, an attenuation of random and external noise, or both. It is proposed that REM sleep refines memories by applying signal gain and attenuating interference, increasing both the signal-to-noise and signal-to-interference ratios. It may be that NREM sleep gain or attenuation is multiplicative such that levels of stronger and weaker or interfering memory traces are differentially affected, but selective processing in REM sleep is thought to be more critical in separating signal and interference traces and contributing to memory fidelity.

Potential mechanisms should be considered. NREM sleep memory reinforcement is thought to occur through repeated experience-dependent offline memory reactivations coordinated by slow wave activity, sharp wave ripples, and spindles. These features are thought to maintain the retrievability of a newly acquired memories by converting the early LTP of transient memory traces into long-lasting LTP via protein synthesis, perhaps while also engaging in a relative downscaling of synapses external to the reactivated memories. REM sleep refinement is thought to occur through bidirectional action on these and competing memory traces, including additional potentiation within dominant memory traces and depotentiation of weaker memory traces, perhaps through phase-dependent firing on low frequency REM sleep oscillations.

In what circumstances will the effects of reinforcement or refinement be most apparent? Performance benefits of reinforcement during sleep would be expected for situations in which there are subsequent (i.e., after sleep) challenges to the availability or accessibility of memories, including decay over time and the acquisition of new memories associated with the same retrieval cues. Performance benefits of refinement during sleep would be expected for situations

in which one is tested on their ability to reliably retrieve a dominant memory among highly competitive alternative memories that were likewise acquired before sleep. Such situations would include testing one's performance of difficult motor routines (for which slight errors could be considered an example of retrieving a highly competitive alternative memory), or, for declarative memory, testing one's retrieval of details for which interference from other associations or schema are likely (e.g., details from a passage of prose). Effects of refinement may also include the impaired retrieval of non-dominant memories that would be weakened in favor of dominant memory representations. Respectively attributing these reinforcement and refinement processes to NREM and REM sleep allows one to predict whether a memory tasks will be sensitive to manipulations of and association with each sleep state. Many experimental designs, including those testing recall of word lists, do not result in substantial competition between alternative memory representations acquired before sleep and thus would not be expected to be sensitive to the effects of refinement processes during REM sleep.

The SR2 hypothesis is informed by and compatible with previous hypotheses of sleep and memory. The reinforcement of newly acquired memories during NREM sleep may be considered a product of the systems consolidation process described in the active systems consolidation hypothesis [76,77], and this reinforcement may occur as a result of or alongside the activity-dependent down-selection of synaptic strength proposed in the synaptic homeostasis hypothesis [98]. Memory refinement through REM sleep is consistent with proposals of bidirectional synaptic change during sleep [85,95,96]. Hypotheses claiming that selectivity in memory consolidation occurs through NREM sleep, Giuditta's [72] sequential hypothesis for example, are not inconsistent with the notion of REM sleep refinement. Although the SR2 hypothesis indicates REM sleep as the primary state of bidirectional synaptic change, it may be

that this refinement simply enacts changes selected for during previous periods of NREM sleep, a prospect already proposed by Seibt and Frank [96]. The SR2 hypothesis is also consistent with the notion that complex memory tasks are more sensitive to manipulations of REM sleep [64,68] given that these tasks (e.g., tracing figures through a mirror) are more likely than their simpler counterparts (e.g., direct tracing) to meet the criteria for refinement effect sensitivity described above.

With these hypotheses of sleep and memory introduced, the past research investigating the effects of sleep on the retrieval of newly acquired memories will be reviewed in detail.

Sleep and Memory Relationship

Memory Change Over Sleep

Sleep-dependent memory consolidation has often been studied by comparing the effect of retention periods with sleep to retention periods of wake, sometimes involving sleep deprivation with or without recovery sleep. Sleep results in greater memory performance for studied verbal material, including syllable or word pairs or word lists [1,2,65,103–111] and educational passages of prose [109], an effect that may be most prominent for associative memory rather than item memory [1,82] and when interfering material is learned after the sleep or wake period [112,113, but see 114] but reduced when participants are asked to first retrieve the material without feedback before sleep [109,110]. Sleep also results in greater memory performance for knowledge of a map [62], recollection (but not familiarity-based recognition) of pictures [84], or the locations of objects [115] or faces [116]. For recognition tasks, sleep For procedural memories, sleep results in greater visual texture discrimination [117,118] and better performance of a learned finger tapping sequence [3,4,119] and structurally complex gross motor tasks [120], but these benefits may not extend to all procedural memory tasks [121]. An important study from

Yang et al. [122] examined memory consolidation at the cellular level by measuring postsynaptic dendritic spine formation in the motor cortex of mice after training to run on a rotating rod. Trained mice showed progressive increases in spine formation relative to untrained mice from 6 to 48 hr after rotarod training. Spine formation was both branch-specific in that it was driven specifically by neuronal branches with a relatively high spine formation and task-specific in that later training on backward rotarod running induced spine formation on the branches with previously low spine formation. Critically, 7-hr sleep deprivation after training impaired performance at one and five days post training and reduced both spine formation and new spine survival on high formation branches whilst having no effect on spine formation on low formation branches or spine elimination.

Researchers have used the half-night paradigm to compare the relative effects of NREM slow wave sleep and REM sleep. Early-night sleep rich in slow wave sleep has been found to benefit memory of word pairs [2,61,108], object locations [62], picture-colour associations [123], and visual texture discrimination [100] whereas late-night sleep rich in REM sleep enhances mirror tracing skill [61], memory for prose [especially emotional prose, 124], and the recognition preference for emotional over neutral pictures [123]. Early-night sleep, but not late-night sleep has also been shown to particularly benefit explicit recollection-based memory in word list item recognition and not familiarity-based recognition that does not require associative memory [83]. However, the half-night paradigm cannot firmly dissociate NREM and REM sleep contributions because both states occur in both halves of the night and the design may be confounded by other circadian differences.

NREM Sleep and Memory

A role for NREM sleep in memory is supported by evidence that time spent in post-

learning slow wave sleep has been positively correlated with cued recall of word pairs [107], visuospatial memory [125], and recognition of learned faces and houses [126], and more stage 2 sleep in nap was associated with offline improvements in a finger tapping motor sequence task [127]. Furthermore, suppression of slow wave sleep by acoustic stimulation reduced offline benefits in visual texture discrimination [128] and a visuomotor task [129]. Short naps containing only NREM sleep were beneficial for memory of word pairs and word lists [106,130].

More has been learned about the role of NREM sleep in memory processing by examining how learning and memory relate to the previously described concert of spindles, slow waves, sharp wave ripples, and memory reactivation. NREM sleep is affected by learning experience as evidenced by the reoccurrence during post-learning NREM sleep of specific neuronal activity patterns present during learning in the rodent hippocampus [21–23,131], neocortex [21,122,131,132], and ventral striatum [133], and in human EEG both at the scalp [126] and intracranially [134,135]. Furthermore, there is evidence of increased spindle activity after learning declarative material [136–138] and procedural material [139–143], increased slow wave activity after learning procedural material [143,144], and increased sharp wave ripples in the rat hippocampus after learning declarative material [145,146]. Greater post-learning spindle activity in task-related regions has been associated with greater retention of words learned before sleep [136,147], improved mirror tracing skill [147], and improved motor sequence performance [127]. Greater post learning slow wave activity has been associated with greater word list retention and mirror tracing [147]. Finally, learning-related increases in spindle activity [138,143], slow wave activity [129,143,144,148], and evidence of spontaneous memory reactivation [126] have all been associated with better memory performance. Notably, these learning-related sleep alterations and correlations with performance occur in task-related regions

of the brain. Thus, learning appears to induce changes in NREM sleep physiology that, in turn, relate to better performance outcomes.

Causal evidence for memory reactivation in NREM sleep benefitting performance comes from an experimental technique known as targeted memory reactivation. Rasch et al. [78] had participants learn a procedural finger tapping task and a series of paired two-dimensional object locations (i.e., card matching) while exposed to a rose odour. Re-exposure to the odour during nocturnal slow wave sleep improved performance on the location memory task compared to those not re-exposed, and there was no effect of odour exposure during sleep alone or re-exposure during REM sleep. Odour re-exposure during slow wave sleep results in a significant blood oxygenation level-dependent response in the left anterior hippocampus and protects visuospatial memories from retroactive interference [78,149]. TMR has also benefitted visuospatial memory performance in a within-subjects design in which distinct audio cues were used to cue some memories during the slow wave sleep of a nap [150]. Although Rasch et al. [78] found no procedural memory benefit of cue re-exposure, at least three studies have reported a benefit: Antony et al. [151] did using a design that had participants tap patterns to different melodies and then had one of those melodies played covertly during slow wave sleep; Schönauer et al. [126] did using auditory cues associated with presses of finger tapping sequences presented during the first 2 hr of a sleep period; and Laventure et al. [152] did using a design similar to that of Rasch et al. [78] but with odour re-exposure during stage 2 NREM sleep rather than slow wave sleep. Belal et al. [153] recently found that, after pairing separate motor sequences with separate audio cues, EEG pattern classification could reliably identify the cue presented during NREM sleep based on patterns in sleep EEG following the cue, indicating that memories were indeed reactivated in TMR.

Manipulations of slow waves, spindles, and sharp wave ripples have also been shown to affect memory performance. Online identification and blocking of hippocampal sharp wave ripples in rats were found to reduce daily memory improvements in a radial maze [154]. Ngo et al. [155] found that auditory stimulation timed to positive peak of surface slow oscillations in human slow wave sleep induced a prolonged train of surface slow oscillations, increased amplitude of the surface slow oscillations, increased 12–15 Hz fast sigma power during the positive peak of the surface slow oscillation, and, critically, increase retention of word pairs learned before sleep relative to sham control. In rats, electrical stimulation designed to reinforce coordination between slow waves, spindles, and sharp wave ripples led to improved memory measured via object discrimination [156]. Furthermore, Latchoumane et al. [157] found that optogenetic induction of spindles in phase with the up state of cortical slow oscillations increased triple coupling of slow oscillations, spindles, and ripples and, critically, improved consolidation of contextual fear memory, whereas optogenetic suppression of in-phase spindles impaired consolidation of contextual fear memory. These findings support the abundance of correlational data and further demonstrate a causal link between synchronous oscillations of NREM sleep and memory performance.

The effect of NREM sleep on memory can also be studied at the cellular and molecular level. The low cholinergic activity during slow wave sleep [90] limits induction of LTP during slow wave sleep [158,159] as evidenced by an absence of plasticity-related immediate early gene EGR-1 expression during NREM sleep in rats even after exposure to an enriched environment or induction of hippocampal LTP during wake [160,161]. However, slow wave sleep is associated with increased synthesis of proteins [88,89], including actin [162], which is involved in maintenance of LTP and the modulation of dendritic spines [163]. Yang et al. [122] who

reported sleep deprivation to reduce branch- and task-specific dendritic spine formation in the mouse motor cortex also investigated memory reactivation. Reducing post-running sleep activity of neurons associated with forward-running (i.e., memory reactivation) via either *N*-methyl-D-aspartate receptor blocker MK801 or backward treadmill running halfway through the sleep period also reduced branch-specific dendritic spine formation. Notably, selective deprivation of REM sleep did not disrupt branch-specific spine formation after rotarod training. Thus, there is support for the notion that NREM sleep memory reactivation reinforces memory traces, in part through a stabilizing early LTP into late-LTP, as proposed by Poe et al. [85] and endorsed by the SR2 hypothesis.

REM Sleep and Memory

In rodents [164,165] and in humans [166–168], there have been reports of increased REMs or REM sleep after periods of learning, although this effect appears to be less robust in human studies [139,140,142]. The amount of post-learning REM sleep has been positively associated with performance outcomes in learning a second language [169], Morse code [166], and a finger tapping sequence [3]. There is also some evidence of disruptions to typical memory benefits of sleep in people taking antidepressants known to supress REM sleep [170,171, but see 172]. However, greater REM sleep duration has also been associated with overnight forgetting of low-value items in a visuospatial memory task [173] and overnight decrements in learning how to ride a bicycle with reversed handlebars [174]. In a visual discrimination task of perceptual learning, only naps containing REM sleep reduced the impairing effects of interference introduced before the nap and the extent to which interference impairments were reduced was positively correlated with REM sleep duration in this subgroup [175]. These findings highlight a complex relationship in which REM sleep may be involved in both learning and forgetting [6],

or, in terms of the SR2 hypothesis, the refining of dominant memories through reducing interference caused by existing highly-competitive representations.

Much of the evidence for REM sleep involvement in memory comes from studying the effect of selective deprivation of REM sleep after learning. Early work in animal models, primarily avoidance learning in rodents, showed that REM sleep deprivation impairs performance particularly for more complex, two-way avoidance tasks and when the deprivation technique is applied in time windows in which there would otherwise be a post-learning increase in REM sleep [176]. Studies of selective REM sleep deprivation in humans have yielded mixed results, which could be the result of their typically small sample sizes or important differences in their memory tasks. For overnight retention of verbal declarative memory, impairments from REM sleep deprivation, relative to concurrent or matched NREM awakenings or slow wave sleep deprivation, have been observed for memory of prose [65,66] and words associated with previous personal failure [177] but not neutral word lists [65,178] and word pairs [179,180]. For procedural memories, Karni et al. [117] found overnight improvements in visual discrimination to be blocked by selective deprivation of REM sleep, and Smith and colleagues [reviewed in 64] identified relative overnight impairments from REM sleep deprivation in tapping implicitly learned sequences, mirror tracing, and the Tower of Hanoi puzzle but not in many declarative memory tasks, direct tracing, or the pursuit rotor task. Combined with findings that late-night sleep benefits performance in mirror tracing, but not word pairs or object locations [2,61,62,108], these results are largely consistent with the SR2 hypothesis notion that REM sleep offers memory refinement that is observable in tasks for which target memory representations must be distinguished from highly competitive alternatives (e.g., a direct tracing motions instead of mirror tracing motions or schema-based assumptions instead of details from prose).

Although the mechanisms are less understood than those for NREM sleep, neural oscillations and neuronal firing patterns of REM sleep have been linked to memory processing. Post-training increases in P wave density or P wave generator activity are observed following two-way avoidance training [181,182] and fear extinction training [183], and post-learning increases in P wave density predict retention of avoidance [181] and extinction [183] training. In the rat hippocampus, Louie and Wilson [184] found the neuronal firing patterns during path running to be reproduced in subsequent REM sleep; however such evidence neuronal replay in REM sleep is not reliably detected [e.g., 185]. Not full neuronal replay of firing patterns from wake, but Kumar et al. [186] found evidence suggesting critical memory reactivation occurs in REM sleep within young adult-born neurons (i.e., those formed from adult neurogenesis) in the dentate gyrus. Kumar et al. [186] found that neurons active post shock in a conditioned fear paradigm were more likely to be active during post-learning REM sleep than those not active post shock and that optogenetic inhibition of this reactivation impaired memory consolidation without affecting sleep architecture of EEG power spectra. As previously indicated, whether rat hippocampal cells active during waking exploration of novel and familiar locations fire during the peak or trough of the hippocampal theta rhythm (respectively associated with LTP and long-term depression [47–49]) during REM sleep, was found to depend on the novelty of the associated waking experience with theta peak firing most common for cells which preferentially fired for novel locations and theta trough firing most common for cells which preferentially fired for familiar locations [95]. Boyce et al. [187] provided more causal evidence of theta activity involvement in memory processing, showing that post-learning optogenetic inhibition of the hippocampal theta rhythm in mice impaired subsequent expression of object place recognition and conditioned fear. Indeed, theta rhythm phase specific firing may be critical for consolidation

of fear memories as Kumar et al. [186] found that inducing random activation of young adult-born neurons during REM sleep, not just inhibiting their firing altogether, also impaired memory consolidation. In humans, REM sleep theta power has been associated with recognition of schema-consistent melodies learned before sleep [188] and selectivity of memory for paired associates [189].

REM sleep has been proposed to be an opportune time for synaptic change [76,80,85], a proposal in part due to cholinergic tone being at near-waking levels during REM sleep and substantially higher than during NREM sleep [90]. High cholinergic activity has been shown to support late LTP in the medial prefrontal cortex of anesthetized rats [190], support long-term depression in slices of rat visual cortex [191], and activate plasticity-related immediate early genes, ARC in rats [192], and EGR-1 in human cell cultures [193]. Indeed, there is increased ARC and EGR-1 expression during REM sleep in rats following exposure to novel stimuli [80,160], induced hippocampal LTP [161], or shock avoidance learning [182] and in response to cholinergic activation of P waves [194]. Post-learning increases in ARC are associated with post-learning increases in P wave density [182] and are abolished by elimination of P wave generating cells [194]. In addition, blocking cholinergic activity during post-training REM sleep impairs later performance in a habit-based version of a radial arm maze in rats [195,196]. In humans, blocking cholinergic activity during post-learning late-night sleep, but not wake, reduced offline gains on a newly learned finger tapping task [197], and increasing acetylcholine availability increased offline gains in mirror tracing ability [198].

An understanding of the role of REM sleep in synaptic plasticity and memory processing is greatly informed by a study from Li et al. [199] measuring dendritic spine formation and elimination in the mouse motor cortex. Groups of mice subjected to selective REM sleep

deprivation by gentle handling, compared to no deprivation and similar NREM sleep interruptions, showed reduced elimination of spines that were newly formed after rotarod training whilst there were no differences observed between groups for elimination of existing spines. Newer spines formed after subsequent training on a reversed direction rotarod tended to form near where REM sleep spine elimination occurred, and mice deprived of REM sleep had lower spine formation after reversed rotarod training and impaired performance on the reversed rotarod compared to non-deprived mice, suggesting REM sleep pruning of spines is important for subsequent learning. Of the persistent spines that survived initial pruning, a greater number showed continued survival four days post training in groups with REM sleep compared to mice deprived of REM sleep, an effect attributable to a post-training REM sleep-dependent increase in persistent spine size. Thus, Li et al. [199] found REM sleep to not only prune some newly formed spines but also strengthen other newly formed spines, and both actions were dependent on calcium spikes on apical dendrites during REM sleep. Critically, mice deprived of REM sleep showed less performance improvement over time than mice with REM sleep even 12 hr after recovery from the deprivation manipulation, indicating that optimal memory performance relies on a REM sleep-dependent selective strengthening and weakening of newly formed spines. These findings and others support the notion that REM sleep is a time of bidirectional synaptic change [85,95,96]; here it is proposed that such bidirectional synaptic change results in refined memory traces and greater precision of memory retrieval during performance.

Conclusion

Over a century of research on sleep and memory has made it clear that sleep provides benefits for newly acquired memories. NREM sleep likely acts on memories in part through reactivations of recent experiences within a coordinated concert of neural oscillations. An

associated increase in protein synthesis during NREM sleep may support late LTP within reactivated memory circuits. The mechanisms of REM sleep memory processing are less clear, but REM sleep appears to be a time of bidirectional synaptic change with impacts on learning and memory. These mechanisms may be understood to benefit newly acquired memories, but their precise effects on memory performance are not yet fully understood.

The SR2 hypothesis is an attempt to complement previous hypotheses largely focused on mechanisms by articulating how post-learning sleep affects memory retrieval behaviour, that is to say, benefitting the extent to which newly acquired memories can be retrieved and the precision of that memory retrieval through respective processes of reinforcement and refinement. In line with evidence for memory consolidation during NREM sleep and bidirectional synaptic plasticity of REM sleep, reinforcement is primarily attributed to NREM sleep and refinement is primarily attributed to REM sleep. Plausible neural correlates of NREM sleep reinforcement and REM sleep refinement have been provided by research on synaptic plasticity, particularly work linking NREM sleep to task-specific dendritic spine formation [122] and work linking REM sleep to selective strengthening and weakening of newly formed dendritic spines [199].

Multiple considerations may improve investigation into the effects of sleep on memory retrieval and lead to greater clarity of the precise effects of sleep on cognitive function. Many behavioural effects discussed in this review are based on single or few research studies, some with a concerningly low sample size. This practice is a concern as such effects, even those which are well-cited and shape hypotheses, may fail to replicate [e.g., 114]. To better understand sleep and memory relationships, the field needs to adopt greater standards of practice for reproducibility of science, pre-register protocols and analyses when possible, and place greater value on attempts to replicate results of previous work [200]. In addition, greater attention to the

demands of memory retrieval may better our understanding of the effect of sleep on later retrieval of newly acquired memories. Whether a task challenges the retrievability of a memory via opportunity for decay or new learning and whether a task challenges the precision of memory retrieval via the presence of highly competitive alternative memories may dictate whether NREM or REM sleep contributes significantly to retrieval performance. Continued investigation into not only the mechanisms underlying sleep and memory relationships but also the behavioural impact of sleep on memory retrieval is important for understanding the functional consequences of insufficient or disordered sleep. As NREM sleep and REM sleep may be differently obtained or affected, a greater understanding of specific contributions afforded by these stages would be valuable.

Research Agenda

1. Systematic investigation into how different memory tasks demands can result in different effects of post-learning sleep on memory retrieval will better inform our understanding of the limits and parameters of the effects of sleep on memory.
2. The use of memory tasks which test the precision of memory retrieval (e.g., performance of difficult motor routines or recall of fine details from prose) may uncover subtle effects of post-learning sleep and may be key to understanding the contributions of REM sleep.
3. The development and use of memory tasks with high ecological validity or questionnaires probing daily memory demands and performance could be instrumental in building a greater understanding of memory retrieval deficits resulting from even subtle sleep deficiencies.
4. Greater adoption of research practices favouring reproducibility, greater use of pre-registration, and greater valuing of replication attempts will allow for greater clarity regarding the true effects of sleep on memory performance.

Practice Points

1. The concert of neural oscillations and memory reactivations characteristic of post-learning non-REM sleep contributes to improved memory performance in many conditions, perhaps by increasing or maintaining the retrievability of newly acquired memories.
2. The conditions for which REM sleep aids memory performance are not yet clear, but post-learning REM sleep appears to be most critical for memory performance when there are demands for precision at retrieval, such as when one must select a target memory among highly competitive alternatives.
3. Contributions of post-learning non-REM and REM sleep to memory performance may be complementary in nature; thus, sufficient quantities of both may be required for optimal memory cognitive function.

Conflicts of Interest

The authors do not have any conflicts of interest to disclose.

References

[1] Studte S, Bridger E, Mecklinger A. Nap sleep preserves associative but not item memory performance. Neurobiol Learn Mem 2015;120:84–93. https://doi.org/10.1016/j.nlm.2015.02.012.

[2] Barrett TR, Ekstrand BR. Effect of sleep on memory: III. Controlling for time-of-day effects. J Exp Psychol 1972;96:321–7. https://doi.org/10.1037/h0033625.

[3] Fischer S, Hallschmid M, Elsner AL, Born J. Sleep forms memory for finger skills. Proc Natl Acad Sci 2002;99:11987–11991. http://dx.doi.org/10.1073/pnas.182178199.

[4] Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R. Practice with sleep makes perfect: Sleep-dependent motor skill learning. Neuron 2002;35:205–11. https://doi.org/10.1016/S0896-6273(02)00746-8.

[5] Crick F, Mitchison G. The function of dream sleep. Nature 1983;304:111–114. https://doi.org/10.1038/304111a0.

*[6] Poe GR. Sleep is for forgetting. J Neurosci 2017;37:464–73. https://doi.org/10.1523/JNEUROSCI.0820-16.2017.

[7] Berry RB, Brooks R, Gamaldo CE, Harding S, Marcus C, Vaughn B. The AASM manual for the scoring of sleep and associated events: Rules, terminology, and technical specifications, version 2.2. American Academy of Sleep Medicine; 2015.

[8] Dement W, Kleitman N. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. Electroencephalogr Clin Neurophysiol 1957;9:673–690. http://dx.doi.org/10.1016/0013-4694(57)90088-3.

[9] Williams RL, Agnew Jr HW, Webb WB. Sleep patterns in the young adult female: an EEG study. Electroencephalogr Clin Neurophysiol 1966;20:264–266. http://dx.doi.org/10.1016/0013-4694(66)90092-7.

[10] Fernandez LMJ, Lüthi A. Sleep Spindles: Mechanisms and Functions. Physiol Rev 2019;100:805–68. https://doi.org/10.1152/physrev.00042.2018.

[11] Steriade M, McCormick D, Sejnowski T. Thalamocortical oscillations in the sleeping and aroused brain. Science 1993;262:679. https://doi.org/10.1126/science.8235588.

[12] Cox R, Schapiro AC, Manoach DS, Stickgold R. Individual differences in frequency and topography of slow and fast sleep spindles. Front Hum Neurosci 2017;11:433. https://doi.org/10.3389/fnhum.2017.00433.

[13] Barakat M, Doyon J, Debas K, Vandewalle G, Morin A, Poirier G, et al. Fast and slow spindle involvement in the consolidation of a new motor sequence. Behav Brain Res 2011;217:117–21. https://doi.org/10.1016/j.bbr.2010.10.019.

[14] Cox R, Hofman WF, de Boer M, Talamini LM. Local sleep spindle modulations in relation to specific memory cues. Neuroimage 2014;99:103–110. https://doi.org/10.1016/j.neuroimage.2014.05.028.

[15] Tamaki M, Matsuoka T, Nittono H, Hori T. Fast sleep spindle (13–15 Hz) activity correlates with sleep-dependent improvement in visuomotor performance. Sleep 2008;31:204–211. https://doi.org/10.1093/sleep/31.2.204.

[16] Tamaki M, Matsuoka T, Nittono H, Hori T. Activation of fast sleep spindles at the premotor cortex and parietal areas contributes to motor learning: a study using sLORETA. Clin Neurophysiol 2009;120:878–886. http://dx.doi.org/10.1016/j.clinph.2009.03.006.

[17] Cairney SA, Guttesen A á V, El Marj N, Staresina BP. Memory consolidation is linked to spindle-mediated information processing during sleep. Curr Biol 2018;28:948-954.e4. https://doi.org/10.1016/j.cub.2018.01.087.
[18] Sanchez-Vives MV. Origin and dynamics of cortical slow oscillations. Physiol Sleep 2020;15:217–23. https://doi.org/10.1016/j.cophys.2020.04.005.
[19] Huber R, Ghilardi MF, Massimini M, Ferrarelli F, Riedner BA, Peterson MJ, et al. Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. Nat Neurosci 2006;9:1169–1176. http://dx.doi.org/10.1038/nn1758.
[20] Buzsáki G. Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. Hippocampus 2015;25:1073–188. https://doi.org/10.1002/hipo.22488.
[21] Ji D, Wilson M. Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 2007;10:100–7. https://doi.org/10.1038/nn1825.
[22] Nádasdy Z, Hirase H, Czurkó A, Csicsvari J, Buzsáki G. Replay and time compression of recurring spike sequences in the hippocampus. J Neurosci 1999;19:9497–9507. http://dx.doi.org/10.1523/JNEUROSCI.19-21-09497.1999.
[23] Wilson MA, McNaughton BL. Reactivation of hippocampal ensemble memories during sleep. Science 1994;265:676–9. https://doi.org/10.1126/science.8036517.
[24] Gridchyn I, Schoenenberger P, O'Neill J, Csicsvari J. Assembly-Specific Disruption of Hippocampal Replay Leads to Selective Memory Deficit. Neuron 2020;106:291-300.e6. https://doi.org/10.1016/j.neuron.2020.01.021.
[25] Clemens Z, Molle M, Eross L, Barsi P, Halasz P, Born J. Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. Brain 2007;130:2868–78. https://doi.org/10.1093/brain/awm146.
[26] Sirota A, Csicsvari J, Buhl D, Buzsaki G. Communication between neocortex and hippocampus during sleep in rodents. Proc Natl Acad Sci U S A 2003;100:2065–9. https://doi.org/10.1073/pnas.0437938100.
[27] Staresina BP, Bergmann TO, Bonnefond M, van der Meij R, Jensen O, Deuker L, et al. Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. Nat Neurosci 2015;18:1679–86. https://doi.org/10.1038/nn.4119.
[28] Mölle M, Marshall L, Gais S, Born J. Grouping of spindle activity during slow oscillations in human non-rapid eye movement sleep. J Neurosci 2002;22:10941–10947. http://dx.doi.org/10.1523/JNEUROSCI.22-24-10941.2002.
[29] Steriade M, Nuñez A, Amzica F. Intracellular analysis of relations between the slow (< 1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. J Neurosci 1993;13:3266–3283. http://dx.doi.org/10.1523/JNEUROSCI.13-08-03266.1993.
[30] Buzsáki G. Theta oscillations in the hippocampus. Neuron 2002;33:325–340. https://doi.org/10.1016/S0896-6273(02)00586-X.
[31] Nowacka A, Jurkowlaniec E, Trojniar W. Microinjection of procaine into the pedunculopontine tegmental nucleus suppresses hippocampal theta rhythm in urethane-anesthetized rats. Brain Res Bull 2002;58:377–384. https://doi.org/10.1016/s0361-9230(02)00801-8.
[32] Datta S, Siwek DF. Excitation of the brain stem pedunculopontine tegmentum cholinergic cells induces wakefulness and REM sleep. J Neurophysiol 1997;77:2975–2988. http://dx.doi.org/10.1152/jn.1997.77.6.2975.

[33] Lesting J, Narayanan RT, Kluge C, Sangha S, Seidenbecher T, Pape H-C. Patterns of coupled theta activity in amygdala-hippocampal-prefrontal cortical circuits during fear extinction. PloS One 2011;6:e21714. https://doi.org/10.1371/journal.pone.0021714.
[34] Popa D, Duvarci S, Popescu AT, Lena C, Pare D. Coherent amygdalocortical theta promotes fear memory consolidation during paradoxical sleep. Proc Natl Acad Sci 2010;107:6516–9. https://doi.org/10.1073/pnas.0913016107.
[35] Siapas AG, Lubenov EV, Wilson MA. Prefrontal phase locking to hippocampal theta oscillations. Neuron 2005;46:141–51. https://doi.org/10.1016/j.neuron.2005.02.028.
[36] Lega BC, Jacobs J, Kahana M. Human hippocampal theta oscillations and the formation of episodic memories. Hippocampus 2012;22:748–761. http://dx.doi.org/10.1002/hipo.20937.
[37] Moroni F, Nobili L, Curcio G, De Carli F, Fratello F, Marzano C, et al. Sleep in the human hippocampus: a stereo-EEG study. PloS One 2007;2:e867. https://doi.org/10.1371/journal.pone.0000867.
[38] Bódizs R, Kántor S, Szabó G, Szûcs A, Erõss L, Halász P. Rhythmic hippocampal slow oscillation characterizes REM sleep in humans. Hippocampus 2001;11:747–53. https://doi.org/10.1002/hipo.1090.
[39] Datta S. Cellular basis of pontine ponto-geniculo-occipital wave generation and modulation. Cell Mol Neurobiol 1997;17:341–365. https://doi.org/10.1023/A:1026398402985.
[40] Gott JA, Liley DTJ, Hobson JA. Towards a functional understanding of PGO waves. Front Hum Neurosci 2017;11:89. https://doi.org/10.3389/fnhum.2017.00089.
[41] Jouvet M. Recherches sur les structures nerveuses et les mécanismes responsables des différentes phases du sommeil physiologique. Arch Ital Biol 1962;100:125–206. https://doi.org/10.4449/aib.v100i2.1761.
[42] Fernández-Mendoza J, Lozano B, Seijo F, Santamarta-Liébana E, José Ramos-Platón M, Vela-Bueno A, et al. Evidence of subthalamic PGO-like waves during REM sleep in humans: a deep brain polysomnographic study. Sleep 2009;32:1117–1126. https://doi.org/10.1093/sleep/32.9.1117.
[43] Lim AS, Lozano AM, Moro E, Hamani C, Hutchison WD, Dostrovsky JO, et al. Characterization of REM-sleep associated ponto-geniculo-occipital waves in the human pons. Sleep 2007;30:823–827. http://dx.doi.org/10.1093/sleep/30.7.823.
[44] Karashima A, Nakamura K, Watanabe M, Sato N, Nakao M, Katayama N, et al. Synchronization between hippocampal theta waves and PGO waves during REM sleep. Psychiatry Clin Neurosci 2001;55:189–190. http://dx.doi.org/10.1046/j.1440-1819.2001.00820.x.
[45] Karashima A, Katayama N, Nakao M. Phase-locking of spontaneous and tone-elicited pontine waves to hippocampal theta waves during REM sleep in rats. Brain Res 2007;1182:73–81. https://doi.org/10.1016/j.brainres.2007.08.060.
[46] Shaffery JP, Roffwarg HP, Speciale SG, Marks GA. Ponto-geniculo-occipital-wave suppression amplifies lateral geniculate nucleus cell-size changes in monocularly deprived kittens. Dev Brain Res 1999;114:109–19. https://doi.org/10.1016/s0165-3806(99)00027-9.
[47] Hölscher C, Anwyl R, Rowan MJ. Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo. J Neurosci 1997;17:6470–6477. http://dx.doi.org/10.1523/JNEUROSCI.17-16-06470.1997.

[48] Huerta PT, Lisman JE. Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. Neuron 1995;15:1053–1063. http://dx.doi.org/10.1016/0896-6273(95)90094-2.
[49] Pavlides C, Greenstein YJ, Grudman M, Winson J. Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of θ-rhythm. Brain Res 1988;439:383–387. http://dx.doi.org/10.1016/0006-8993(88)91499-0.
[50] Squire LR, Genzel L, Wixted JT, Morris RG. Memory consolidation. Cold Spring Harb Perspect Biol 2015;7:a021766. https://doi.org/10.1101/cshperspect.a021766.
[51] Squire LR, Knowlton B, Musen G. The structure and organization of memory. Annu Rev Psychol 1993;44:453–495. https://doi.org/10.1146/annurev.ps.44.020193.002321.
[52] Tulving E, Le Voi ME, Routh DA, Loftus E, Broadbent DE. Ecphoric processes in episodic memory. Philos Trans R Soc Lond B Biol Sci 1983;302:361–71. https://doi.org/10.1098/rstb.1983.0060.
[53] Frankland PW, Josselyn SA, Köhler S. The neurobiological foundation of memory retrieval. Nat Neurosci 2019;22:1576–85. https://doi.org/10.1038/s41593-019-0493-1.
[54] Anderson MC, Neely JH. Interference and Inhibition in Memory Retrieval. In: Bjork EL, Bjork RA, editors. Memory, San Diego: Academic Press; 1996, p. 237–313. https://doi.org/10.1016/B978-012102570-0/50010-0.
[55] Oberauer K, Lin H-Y. An interference model of visual working memory. Psychol Rev 2017;124:21–59. https://doi.org/10.1037/rev0000044.
[56] Baltaci SB, Mogulkoc R, Baltaci AK. Molecular mechanisms of early and late LTP. Neurochem Res 2019;44:281–96. https://doi.org/10.1007/s11064-018-2695-4.
[57] Collingridge GL, Peineau S, Howland JG, Wang YT. Long-term depression in the CNS. Nat Rev Neurosci 2010;11:459–473. https://doi.org/10.1038/nrn2867.
[58] Chidambaram SB, Rathipriya AG, Bolla SR, Bhat A, Ray B, Mahalakshmi AM, et al. Dendritic spines: Revisiting the physiological role. Prog Neuropsychopharmacol Biol Psychiatry 2019;92:161–93. https://doi.org/10.1016/j.pnpbp.2019.01.005.
[59] Gais S, Born J. Declarative memory consolidation: mechanisms acting during human sleep. Learn Mem 2004;11:679–685. http://dx.doi.org/10.1101/lm.80504.
[60] Peigneux P, Laureys S, Delbeuck X, Maquet P. Sleeping brain, learning brain. The role of sleep for memory systems. Neuroreport 2001;12:A111–A124. https://doi.org/10.1097/00001756-200112210-00001.
[61] Plihal W, Born J. Effects of early and late nocturnal sleep on declarative and procedural memory. J Cogn Neurosci 1997;9:534–47. https://doi.org/10.1162/jocn.1997.9.4.534.
[62] Plihal W, Born J. Effects of early and late nocturnal sleep on priming and spatial memory. Psychophysiology 1999;36:571–582. https://doi.org/10.1111/1469-8986.3650571.
[63] Smith C, MacNeill C. Impaired motor memory for a pursuit rotor task following Stage 2 sleep loss in college students. J Sleep Res 1994;3:206–213. http://dx.doi.org/10.1111/j.1365-2869.1994.tb00133.x.
*[64] Smith CT, Aubrey JB, Peters KR. Different roles for REM and stage 2 sleep in motor learning: A proposed model. Psychol Belg 2004;44:81–104.
[65] Empson J, Clarke P. Rapid eye movements and remembering. Nature 1970;227:287–288. http://dx.doi.org/10.1038/227287a0.
[66] Tilley AJ, Empson JA. REM sleep and memory consolidation. Biol Psychol 1978;6:293–300. http://dx.doi.org/10.1016/0301-0511(78)90031-5.

[67] De Koninck J, Lorrain D, Christ G, Proulx G, Coulombe D. Intensive language learning and increases in rapid eye movement sleep: evidence of a performance factor. Int J Psychophysiol 1989;8:43–47.
[68] Tilley AJ, Brown S, Donald M, Ferguson S, Piccone J, Plasto K, et al. Human sleep and memory processes. In: Broughton RJ, Ogilvie RD, editors. Sleep Arousal Perform. Tribute Bob Wilkinson, Birkhäuser; 1992, p. 117–27.
[69] Genzel L, Spoormaker V, Konrad B, Dresler M. The role of rapid eye movement sleep for amygdala-related memory processing. Neurobiol Learn Mem 2015;122:110–121. https://doi.org/10.1016/j.nlm.2015.01.008.
[70] Ackermann S, Rasch B. Differential effects of non-REM and REM sleep on memory consolidation? Curr Neurol Neurosci Rep 2014;14. https://doi.org/10.1007/s11910-013-0430-8.
[71] Giuditta A. A sequential hypothesis for the function of sleep. In: Koella WP, Ruther E, Schulz H, editors. Sleep ′84, Stuttgart: Fischer Verlag; 1985, p. 222–4.
[72] Giuditta A. Sleep memory processing: the sequential hypothesis. Front Syst Neurosci 2014;8:219. http://dx.doi.org/10.3389/fnsys.2014.00219.
[73] Ficca G, Lombardo P, Rossi L, Salzarulo P. Morning recall of verbal material depends on prior sleep organization. Behav Brain Res 2000;112:159–163. http://dx.doi.org/10.1016/S0166-4328(00)00177-7.
[74] Mazzoni G, Gori S, Formicola G, Gneri C, Massetani R, Murri L, et al. Word recall correlates with sleep cycles in elderly subjects. J Sleep Res 1999;8:185–188. http://dx.doi.org/10.1046/j.1365-2869.1999.00154.x.
[75] Stickgold R, Walker MP. Sleep-dependent memory triage: evolving generalization through selective processing. Nat Neurosci 2013;16:139–45. https://doi.org/10.1038/nn.3303.
[76] Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci 2010;11:114–26. https://doi.org/10.1038/nrn2762.
*[77] Klinzing JG, Niethard N, Born J. Mechanisms of systems memory consolidation during sleep. Nat Neurosci 2019;22:1598–610. https://doi.org/10.1038/s41593-019-0467-3.
[78] Rasch B, Buchel C, Gais S, Born J. Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 2007;315:1426–9. https://doi.org/10.1126/science.1138581.
[79] Helfrich RF, Lendner JD, Mander BA, Guillen H, Paff M, Mnatsakanyan L, et al. Bidirectional prefrontal-hippocampal dynamics organize information transfer during sleep in humans. Nat Commun 2019;10:3572. https://doi.org/10.1038/s41467-019-11444-x.
*[80] Ribeiro S, Shi X, Engelhard M, Zhou Y, Zhang H, Gervasoni D, et al. Novel experience induces persistent sleep-dependent plasticity in the cortex but not in the hippocampus. Front Neurosci 2007;1:43–55. https://doi.org/10.3389/neuro.01.1.1.003.2007.
[81] Yonelinas AP, Ranganath C, Ekstrom AD, Wiltgen BJ. A contextual binding theory of episodic memory: systems consolidation reconsidered. Nat Rev Neurosci 2019;20:364–75. https://doi.org/10.1038/s41583-019-0150-4.
[82] van der Helm E, Gujar N, Nishida M, Walker MP. Sleep-Dependent Facilitation of Episodic Memory Details. PLOS ONE 2011;6:e27421. https://doi.org/10.1371/journal.pone.0027421.
[83] Drosopoulos S, Wagner U, Born J. Sleep enhances explicit recollection in recognition memory. Learn Mem 2005;12:44–51. https://doi.org/10.1101/lm.83805.

[84] Atienza M, Cantero JL. Modulatory effects of emotion and sleep on recollection and familiarity. J Sleep Res 2008;17:285–94. https://doi.org/10.1111/j.1365-2869.2008.00661.x.
*[85] Poe GR, Walsh CM, Bjorness TE. Cognitive neuroscience of sleep. Prog Brain Res 2010;185:1–19. https://doi.org/10.1016/B978-0-444-53702-7.00001-4.
[86] Frey U, Krug M, Reymann KG, Matthies H. Anisomycin, an inhibitor of protein synthesis, blocks late phases of LTP phenomena in the hippocampal CA1 region in vitro. Brain Res 1988;452:57–65. https://doi.org/10.1016/0006-8993(88)90008-x.
[87] Krug M, Lossner B, Ott T. Anisomycin blocks the late phase of long-term potentiation in the dentate gyrus of freely moving rats. Brain Res Bull 1984;13:39–42. https://doi.org/10.1016/0361-9230(84)90005-4.
[88] Nakanishi H, Sun Y, Nakamura RK, Mori K, Ito M, Suda S, et al. Positive correlations between cerebral protein synthesis rates and deep sleep in Macaca mulatta. Eur J Neurosci 1997;9:271–9. https://doi.org/10.1111/j.1460-9568.1997.tb01397.x.
[89] Ramm P, Smith CT. Rates of cerebral protein synthesis are linked to slow wave sleep in the rat. Physiol Behav 1990;48:749–753. http://dx.doi.org/10.1016/0031-9384(90)90220-X.
[90] Marrosu F, Portas C, Mascia MS, Casu MA, Fà M, Giagheddu M, et al. Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats. Brain Res 1995;671:329–332. http://dx.doi.org/10.1016/0006-8993(94)01399-3.
[91] Hasselmo ME, Bower JM. Acetylcholine and memory. Trends Neurosci 1993;16:218–22. https://doi.org/10.1016/0166-2236(93)90159-J.
[92] Aston-Jones G, Bloom F. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J Neurosci 1981;1:876–886. https://doi.org/10.1523/JNEUROSCI.01-08-00876.1981.
[93] Katsuki H, Izumi Y, Zorumski CF. Noradrenergic regulation of synaptic plasticity in the hippocampal CA1 region. J Neurophysiol 1997;77:3013–3020. https://doi.org/10.1152/jn.1997.77.6.3013.
[94] Thomas MJ, Moody TD, Makhinson M, O'Dell TJ. Activity-dependent β-adrenergic modulation of low frequency stimulation induced LTP in the hippocampal CA1 region. Neuron 1996;17:475–482. https://doi.org/10.1016/s0896-6273(00)80179-8.
*[95] Poe GR, Nitz DA, McNaughton BL, Barnes CA. Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. Brain Res 2000;855:176–180. http://dx.doi.org/10.1016/S0006-8993(99)02310-0.
[96] Seibt J, Frank MG. Primed to sleep: The dynamics of synaptic plasticity across brain states. Front Syst Neurosci 2019;13. https://doi.org/10.3389/fnsys.2019.00002.
[97] Giuditta A. Sleep memory processing: the sequential hypothesis. Front Syst Neurosci 2014;8. https://doi.org/10.3389/fnsys.2014.00219.
[98] Tononi G, Cirelli C. Sleep and the Price of Plasticity: From Synaptic and Cellular Homeostasis to Memory Consolidation and Integration. Neuron 2014;81:12–34. https://doi.org/10.1016/j.neuron.2013.12.025.
[99] Léna I, Parrot S, Deschaux O, Muffat-Joly S, Sauvinet V, Renaud B, et al. Variations in extracellular levels of dopamine, noradrenaline, glutamate, and aspartate across the sleep--wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. J Neurosci Res 2005;81:891–9. https://doi.org/10.1002/jnr.20602.

[100] Gais S, Plihal W, Wagner U, Born J. Early sleep triggers memory for early visual discrimination skills. Nat Neurosci 2000;3:1335. https://doi.org/10.1038/81881.
[101] Mednick S, Nakayama K, Stickgold R. Sleep-dependent learning: a nap is as good as a night. Nat Neurosci 2003;6:697–8. https://doi.org/10.1038/nn1078.
[102] Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA. Visual discrimination task improvement: A multi-step process occurring during sleep. J Cogn Neurosci 2000;12:246–254. https://doi.org/10.1162/089892900562075.
[103] Benson K, Feinberg I. The beneficial effect of sleep in an extended Jenkins and Dallenbach paradigm. Psychophysiology 1977;14:375–384. https://doi.org/10.1111/j.1469-8986.1977.tb02967.x.
[104] Grosvenor A, Lack LC. The effect of sleep before or after learning on memory. Sleep 1984;7:155–167. http://dx.doi.org/10.1093/sleep/7.2.155.
[105] Jenkins JG, Dallenbach KM. Obliviscence during sleep and waking. Am J Psychol 1924;35:605–12.
[106] Lahl O, Wispel C, Willigens B, Pietrowsky R. An ultra short episode of sleep is sufficient to promote declarative memory performance. J Sleep Res 2008;17:3–10. https://doi.org/10.1111/j.1365-2869.2008.00622.x.
[107] Schabus M, Hödlmoser K, Pecherstorfer T, Klösch G. Influence of midday naps on declarative memory performance and motivation. Somnologie-Schlafforschung Schlafmed 2005;9:148–153. https://doi.org/10.1111/j.1439-054X.2005.00054.x.
[108] Yaroush R, Sullivan MJ, Ekstrand BR. Effect of sleep on memory: II. Differential effect of the first and second half of the night. J Exp Psychol 1971;88:361–366. http://dx.doi.org/10.1037/h0030914.
[109] Bäuml K-HT, Holterman C, Abel M. Sleep can reduce the testing effect: It enhances recall of restudied items but can leave recall of retrieved items unaffected. J Exp Psychol Learn Mem Cogn 2014;40:1568–81. https://doi.org/10.1037/xlm0000025.
[110] Abel M, Haller V, Köck H, Pötschke S, Heib D, Schabus M, et al. Sleep reduces the testing effect—But not after corrective feedback and prolonged retention interval. J Exp Psychol Learn Mem Cogn 2019;45:272–87. https://doi.org/10.1037/xlm0000576.
[111] Drosopoulos S, Schulze C, Fischer S, Born J. Sleep's function in the spontaneous recovery and consolidation of memories. J Exp Psychol Gen 2007;136:169–83. https://doi.org/10.1037/0096-3445.136.2.169.
[112] Ellenbogen JM, Hulbert JC, Stickgold R, Dinges DF, Thompson-Schill SL. Interfering with theories of sleep and memory: Sleep, declarative memory, and associative interference. Curr Biol 2006;16:1290–4. https://doi.org/10.1016/j.cub.2006.05.024.
[113] Ellenbogen J, Hulbert J, Jiang Y, Stickgold R. The Sleeping Brain's Influence on Verbal Memory: Boosting Resistance to Interference. PLOS ONE 2009;4.
[114] Bailes C, Caldwell M, Wamsley EJ, Tucker MA. Does sleep protect memories against interference? A failure to replicate. PLOS ONE 2020;15:e0220419. https://doi.org/10.1371/journal.pone.0220419.
[115] Wilhelm I, Diekelmann S, Born J. Sleep in children improves memory performance on declarative but not procedural tasks. Learn Mem 2008;15:373–7. https://doi.org/10.1101/lm.803708.
[116] Talamini LM, Nieuwenhuis ILC, Takashima A, Jensen O. Sleep directly following learning benefits consolidation of spatial associative memory. Learn Mem 2008;15:233–7. https://doi.org/10.1101/lm.771608.

[117] Karni A, Tanne D, Rubenstein BS, Askenasy J JM, Sagi D. Dependence on REM sleep of overnight improvement of a perceptual skill. Science 1994;265:679–82. https://doi.org/10.1126/science.8036518.
[118] Stickgold R, James L, Hobson JA. Visual discrimination learning requires sleep after training. Nat Neurosci 2000;3:1237–8. https://doi.org/10.1038/81756.
[119] Korman M, Doyon J, Doljansky J, Carrier J, Dagan Y, Karni A. Daytime sleep condenses the time course of motor memory consolidation. Nat Neurosci 2007;10:1206–13. https://doi.org/10.1038/nn1959.
[120] Blischke K, Malangré A. Task Complexity Modulates Sleep-Related Offline Learning in Sequential Motor Skills. Front Hum Neurosci 2017;11:374. https://doi.org/10.3389/fnhum.2017.00374.
[121] Robertson EM, Pascual-Leone A, Miall RC. Current concepts in procedural consolidation. Nat Rev Neurosci 2004;5:576–82. https://doi.org/10.1038/nrn1426.
*[122] Yang G, Lai CSW, Cichon J, Ma L, Li W, Gan W-B. Sleep promotes branch-specific formation of dendritic spines after learning. Science 2014;344:1173–1178. http://dx.doi.org/10.1126/science.1249098.
[123] Groch S, Zinke K, Wilhelm I, Born J. Dissociating the contributions of slow-wave sleep and rapid eye movement sleep to emotional item and source memory. Neurobiol Learn Mem 2015;122:122–30. https://doi.org/10.1016/j.nlm.2014.08.013.
[124] Wagner U, Gais S, Born J. Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. Learn Mem 2001;8:112–9. https://doi.org/10.1101/lm.36801.
[125] Diekelmann S, Biggel S, Rasch B, Born J. Offline consolidation of memory varies with time in slow wave sleep and can be accelerated by cuing memory reactivations. Neurobiol Learn Mem 2012;98:103–11. https://doi.org/10.1016/j.nlm.2012.07.002.
[126] Schönauer M, Alizadeh S, Jamalabadi H, Abraham A, Pawlizki A, Gais S. Decoding material-specific memory reprocessing during sleep in humans. Nat Commun 2017;8:15404. https://doi.org/10.1038/ncomms15404.
[127] Nishida M, Walker MP. Daytime naps, motor memory consolidation and regionally specific sleep spindles. PLoS ONE 2007;2:e341. https://doi.org/10.1371/journal.pone.0000341.
[128] Aeschbach D, Cutler AJ, Ronda JM. A role for non-rapid-eye-movement sleep homeostasis in perceptual learning. J Neurosci 2008;28:2766–72. https://doi.org/10.1523/JNEUROSCI.5548-07.2008.
[129] Landsness EC, Crupi D, Hulse BK, Peterson MJ, Huber R, Ansari H, et al. Sleep-dependent improvement in visuomotor learning: a causal role for slow waves. Sleep 2009;32:1273–1284. https://doi.org/10.1093/sleep/32.10.1273.
[130] Tucker MA, Fishbein W. Enhancement of declarative memory performance following a daytime nap is contingent on strength of initial task acquisition. Sleep 2008;31:197–203. https://doi.org/10.1093/sleep/31.2.197.
[131] Qin Y-L, McNaughton BL, Skaggs WE, Barnes CA. Memory reprocessing in corticocortical and hippocampocortical neuronal ensembles. Philos Trans R Soc Lond B Biol Sci 1997;352:1525–1533. http://dx.doi.org/10.1098/rstb.1997.0139.
[132] Hoffman K, McNaughton B. Coordinated reactivation of distributed memory traces in primate neocortex. Science 2002;297:2070–2073. http://dx.doi.org/10.1126/science.1073538.

[133] Lansink CS, Goltstein PM, Lankelma JV, Joosten RNJMA, McNaughton BL, Pennartz CMA. Preferential reactivation of motivationally relevant information in the ventral striatum. J Neurosci 2008;28:6372–82. https://doi.org/10.1523/JNEUROSCI.1054-08.2008.
[134] Zhang H, Fell J, Axmacher N. Electrophysiological mechanisms of human memory consolidation. Nat Commun 2018;9:4103. https://doi.org/10.1038/s41467-018-06553-y.
[135] Eichenlaub J-B, Biswal S, Peled N, Rivilis N, Golby AJ, Lee JW, et al. Reactivation of Motor-Related Gamma Activity in Human NREM Sleep. Front Neurosci 2020;14:449–449. https://doi.org/10.3389/fnins.2020.00449.
[136] Clemens Z, Fabó D, Halász P. Overnight verbal memory retention correlates with the number of sleep spindles. Neuroscience 2005;132:529–35. https://doi.org/10.1016/j.neuroscience.2005.01.011.
[137] Meier-Koll A, Bussmann B, Schmidt C, Neuschwander D. Walking through a maze alters the architecture of sleep. Percept Mot Skills 1999;88:1141–59. https://doi.org/10.2466/pms.1999.88.3c.1141.
[138] Schabus M, Gruber G, Parapatics S, Sauter C, Klösch G, Anderer P, et al. Sleep spindles and their significance for declarative memory consolidation. Sleep 2004;27:1479–1485. http://dx.doi.org/10.1093/sleep/27.7.1479.
[139] Fogel S, Smith C, Cote K. Dissociable learning-dependent changes in REM and non-REM sleep in declarative and procedural memory systems. Behav Brain Res 2007;180:48–61. https://doi.org/10.1016/j.bbr.2007.02.037.
[140] Fogel SM, Smith CT. Learning-dependent changes in sleep spindles and stage 2 sleep. J Sleep Res 2006;15:250–255. http://dx.doi.org/10.1111/j.1365-2869.2006.00522.x.
[141] Morin A, Doyon J, Dostie V, Barakat M, Hadj Tahar A, Korman M, et al. Motor sequence learning increases sleep spindles and fast frequencies in post-training sleep. Sleep 2008;31:1149–56. https://doi.org/10.5665/sleep/31.8.1149.
[142] Peters KR, Ray L, Smith V, Smith C. Changes in the density of stage 2 sleep spindles following motor learning in young and older adults. J Sleep Res 2008;17:23–33. https://doi.org/10.1111/j.1365-2869.2008.00634.x.
[143] Tamaki M, Huang T-R, Yotsumoto Y, Hamalainen M, Lin F-H, Nanez JE, et al. Enhanced spontaneous oscillations in the supplementary motor area are associated with sleep-dependent offline learning of finger-tapping motor-sequence task. J Neurosci 2013;33:13894–902. https://doi.org/10.1523/JNEUROSCI.1198-13.2013.
[144] Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. Nature 2004;430:78–81. http://dx.doi.org/10.1038/nature02663.
[145] Eschenko O, Ramadan W, Molle M, Born J, Sara SJ. Sustained increase in hippocampal sharp-wave ripple activity during slow-wave sleep after learning. Learn Mem 2008;15:222–8. https://doi.org/10.1101/lm.726008.
[146] Mölle M, Eschenko O, Gais S, Sara SJ, Born J. The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. Eur J Neurosci 2009;29:1071–81. https://doi.org/10.1111/j.1460-9568.2009.06654.x.
[147] Holz J, Piosczyk H, Feige B, Spiegelhalder K, Baglioni C, Riemann D, et al. EEG sigma and slow-wave activity during NREM sleep correlate with overnight declarative and procedural memory consolidation: EEG sigma and SWA and memory consolidation. J Sleep Res 2012;21:612–9. https://doi.org/10.1111/j.1365-2869.2012.01017.x.

[148] Ruch S, Markes O, Duss SB, Oppliger D, Reber TP, Koenig T, et al. Sleep stage II contributes to the consolidation of declarative memories. Neuropsychologia 2012;50:2389–96. https://doi.org/10.1016/j.neuropsychologia.2012.06.008.
[149] Diekelmann S, Büchel C, Born J, Rasch B. Labile or stable: opposing consequences for memory when reactivated during waking and sleep. Nat Neurosci 2011;14:381–6. https://doi.org/10.1038/nn.2744.
[150] Rudoy JD, Voss JL, Westerberg CE, Paller KA. Strengthening individual memories by reactivating them during sleep. Science 2009;326:1079–1079. https://doi.org/10.1126/science.1179013.
[151] Antony JW, Gobel EW, O'Hare JK, Reber PJ, Paller KA. Cued memory reactivation during sleep influences skill learning. Nat Neurosci 2012;15:1114–6. https://doi.org/10.1038/nn.3152.
[152] Laventure S, Fogel S, Lungu O, Albouy G, Sévigny-Dupont P, Vien C, et al. NREM2 and sleep spindles are instrumental to the consolidation of motor sequence memories. PLoS One 2016;14:e1002429. https://doi.org/10.1371/journal.pbio.1002429.
[153] Belal S, Cousins J, El-Deredy W, Parkes L, Schneider J, Tsujimura H, et al. Identification of memory reactivation during sleep by EEG classification. NeuroImage 2018;176:203–14. https://doi.org/10.1016/j.neuroimage.2018.04.029.
[154] Girardeau G, Benchenane K, Wiener SI, Buzsáki G, Zugaro MB. Selective suppression of hippocampal ripples impairs spatial memory. Nat Neurosci 2009;12:1222–3. https://doi.org/10.1038/nn.2384.
[155] Ngo H-VV, Martinetz T, Born J, Mölle M. Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron 2013;78:545–53. https://doi.org/10.1016/j.neuron.2013.03.006.
[156] Maingret N, Girardeau G, Todorova R, Goutierre M, Zugaro M. Hippocampo-cortical coupling mediates memory consolidation during sleep. Nat Neurosci 2016;19:959–64. https://doi.org/10.1038/nn.4304.
[157] Latchoumane C-FV, Ngo H-VV, Born J, Shin H-S. Thalamic Spindles Promote Memory Formation during Sleep through Triple Phase-Locking of Cortical, Thalamic, and Hippocampal Rhythms. Neuron 2017;95:424-435.e6. https://doi.org/10.1016/j.neuron.2017.06.025.
[158] Bramham CR, Srebro B. Synaptic plasticity in the hippocampus is modulated by behavioral state. Brain Res 1989;493:74–86. https://doi.org/10.1016/0006-8993(89)91001-9.
[159] Leonard BJ, McNaughton BL, Barnes CA. Suppression of hippocampal synaptic plasticity during slow-wave sleep. Brain Res 1987;425:174–7. https://doi.org/10.1016/0006-8993(87)90496-3.
[160] Ribeiro S, Goyal V, Mello CV, Pavlides C. Brain gene expression during REM sleep depends on prior waking experience. Learn Mem 1999;6:500–508. http://dx.doi.org/10.1101/lm.6.5.500.
[161] Ribeiro S, Mello CV, Velho T, Gardner TJ, Jarvis ED, Pavlides C. Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. J Neurosci 2002;22:10914–10923. https://doi.org/10.1523/JNEUROSCI.22-24-10914.2002.

[162] Vazquez J, Hall SC, Witkowska HE, Greco MA. Rapid alterations in cortical protein profiles underlie spontaneous sleep and wake bouts. J Cell Biochem 2008;105:1472–84. https://doi.org/10.1002/jcb.21970.
[163] Bramham CR. Local protein synthesis, actin dynamics, and LTP consolidation. Curr Opin Neurobiol 2008;18:524–31. https://doi.org/10.1016/j.conb.2008.09.013.
[164] Destrade C, Hennevin E, Leconte P, Soumireu-Mourat B. Relationship between paradoxical sleep and time-dependent improvement of performance in BALB/c mice. Neurosci Lett 1978;7:239–244. http://dx.doi.org/10.1016/0304-3940(78)90175-1.
[165] Smith C, Young J, Young W. Prolonged increases in paradoxical sleep during and after avoidance-task acquisition. Sleep 1980;3:67–81. https://doi.org/10.1093/sleep/3.1.67.
[166] Mandai O, Guerrien A, Sockeel P, Dujardin K, Leconte P. REM sleep modifications following a Morse code learning session in humans. Physiol Behav 1989;46:639–642. http://dx.doi.org/10.1016/0031-9384(89)90344-2.
[167] Smith C, Lapp L. Increases in number of REMS and REM density in humans following an intensive learning period. Sleep 1991;14:325–30. https://doi.org/10.1093/sleep/14.4.325.
[168] Verschoor GJ, Holdstock TL. REM bursts and REM sleep following visual and auditory learning. South Afr J Psychol 1984;14:69–74. http://dx.doi.org/10.1177/008124638401400301.
[169] De Koninck J, Christ G, Hebert G, Rinfret N. Language learning efficiency, dreams and REM sleep. Psychiatr J Univ Ott 1990;15:91–2.
[170] Genzel L, Ali E, Dresler M, Steiger A, Tesfaye M. Sleep-dependent memory consolidation of a new task is inhibited in psychiatric patients. J Psychiatr Res 2011;45:555–60. https://doi.org/10.1016/j.jpsychires.2010.08.015.
[171] Goerke M, Cohrs S, Rodenbeck A, Kunz D. Differential effect of an anticholinergic antidepressant on sleep-dependent memory consolidation. Sleep 2014;37:977–85. https://doi.org/10.5665/sleep.3674.
[172] Rasch B, Pommer J, Diekelmann S, Born J. Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. Nat Neurosci 2009;12:396–7. https://doi.org/10.1038/nn.2206.
[173] Oudiette D, Antony JW, Creery JD, Paller KA. The role of memory reactivation during wakefulness and sleep in determining which memories endure. J Neurosci 2013;33:6672–8. https://doi.org/10.1523/JNEUROSCI.5497-12.2013.
*[174] Hoedlmoser K, Birklbauer J, Schabus M, Eibenberger P, Rigler S, Mueller E. The impact of diurnal sleep on the consolidation of a complex gross motor adaptation task. J Sleep Res 2015;24:100–9. https://doi.org/10.1111/jsr.12207.
*[175] McDevitt EA, Duggan KA, Mednick SC. REM sleep rescues learning from interference. REM Sleep Mem 2015;122:51–62. https://doi.org/10.1016/j.nlm.2014.11.015.
[176] Smith C. Sleep states and learning: a review of the animal literature. Neurosci Biobehav Rev 1985;9:157–168. https://doi.org/10.1016/0149-7634(85)90042-9.
[177] Grieser C, Greenberg R, Harrison RH. The adaptive function of sleep: the differential effects of sleep and dreaming on recall. J Abnorm Psychol 1972;80:280–6. https://doi.org/10.1037/h0033641.
[178] Lewin I, Glaubman H. The effect of REM deprivation: is it detrimental, beneficial, or neutral? Psychophysiology 1975;12:349–353. http://dx.doi.org/10.1111/j.1469-8986.1975.tb01303.x.

[179] Chernik D. Effect of REM sleep deprivation on learning and recall by humans. Percept Mot Skills 1972;34:283–294. https://doi.org/10.2466/pms.1972.34.1.283.
[180] Ekstrand BR, Sullivan MJ, Parker DF, West JN. Spontaneous recovery and sleep. J Exp Psychol 1971;88:142–4. https://doi.org/10.1037/h0030642.
[181] Datta S. Avoidance task training potentiates phasic pontine-wave density in the rat: a mechanism for sleep-dependent plasticity. J Neurosci 2000;20:8607–8613. https://doi.org/10.1523/JNEUROSCI.20-22-08607.2000.
[182] Ulloor J, Datta S. Spatio-temporal activation of cyclic AMP response element-binding protein, activity-regulated cytoskeletal-associated protein and brain-derived nerve growth factor: a mechanism for pontine-wave generator activation-dependent two-way active-avoidance memory processing in the rat. J Neurochem 2005;95:418–28. https://doi.org/10.1111/j.1471-4159.2005.03378.x.
[183] Datta S, O'Malley MW. Fear extinction memory consolidation requires potentiation of pontine-wave activity during REM sleep. J Neurosci 2013;33:4561–9. https://doi.org/10.1523/JNEUROSCI.5525-12.2013.
[184] Louie K, Wilson MA. Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron 2001;29:145–156. http://dx.doi.org/10.1016/S0896-6273(01)00186-6.
[185] Kudrimoti HS, Barnes CA, McNaughton BL. Reactivation of Hippocampal Cell Assemblies: Effects of Behavioral State, Experience, and EEG Dynamics. J Neurosci 1999;19:4090. https://doi.org/10.1523/JNEUROSCI.19-10-04090.1999.
[186] Kumar D, Koyanagi I, Carrier-Ruiz A, Vergara P, Srinivasan S, Sugaya Y, et al. Sparse Activity of Hippocampal Adult-Born Neurons during REM Sleep Is Necessary for Memory Consolidation. Neuron 2020;107:552-565.e10. https://doi.org/10.1016/j.neuron.2020.05.008.
[187] Boyce R, Glasgow SD, Williams S, Adamantidis A. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. Science 2016;352:812–6. https://doi.org/10.1126/science.aad5252.
[188] Durrant SJ, Cairney SA, McDermott C, Lewis PA. Schema-conformant memories are preferentially consolidated during REM sleep. Neurobiol Learn Mem 2015;122:41–50. https://doi.org/10.1016/j.nlm.2015.02.011.
[189] MacDonald KJ, Cote KA. Sleep physiology predicts memory retention after reactivation. J Sleep Res 2016;25:655–63. https://doi.org/10.1111/jsr.12423.
[190] Lopes Aguiar C, Romcy-Pereira RN, Escorsim Szawka R, Galvis-Alonso OY, Anselmo-Franci JA, Pereira Leite J. Muscarinic acetylcholine neurotransmission enhances the late-phase of long-term potentiation in the hippocampal-prefrontal cortex pathway of rats in vivo: a possible involvement of monoaminergic systems. Neuroscience 2008;153:1309–19. https://doi.org/10.1016/j.neuroscience.2008.02.040.
[191] Kirkwood A, Rozas C, Kirkwood J, Perez F, Bear MF. Modulation of long-term synaptic depression in visual cortex by acetylcholine and norepinephrine. J Neurosci 1999;19:1599–1609. http://dx.doi.org/10.1523/JNEUROSCI.19-05-01599.1999.
[192] Teber I, Köhling R, Speckmann E-J, Barnekow A, Kremerskothen J. Muscarinic acetylcholine receptor stimulation induces expression of the activity-regulated cytoskeleton-associated gene (ARC). Mol Brain Res 2004;121:131–6. https://doi.org/10.1016/j.molbrainres.2003.11.017.

[193] von der Kammer H, Mayhaus M, Albrecht C, Enderich J, Wegner M, Nitsch RM. Muscarinic acetylcholine receptors activate expression of the EGR gene family of transcription factors. J Biol Chem 1998;273:14538–44. https://doi.org/10.1074/jbc.273.23.14538.
[194] Datta S, Li G, Auerbach S. Activation of phasic pontine-wave generator in the rat: a mechanism for expression of plasticity-related genes and proteins in the dorsal hippocampus and amygdala. Eur J Neurosci 2008;27:1876–92. https://doi.org/10.1111/j.1460-9568.2008.06166.x.
[195] Legault G, Smith CT, Beninger RJ. Scopolamine during the paradoxical sleep window impairs radial arm maze learning in rats. Pharmacol Biochem Behav 2004;79:715–21. https://doi.org/10.1016/j.pbb.2004.09.018.
[196] Legault G, Smith CT, Beninger RJ. Post-training intra-striatal scopolamine or flupenthixol impairs radial maze learning in rats. Behav Brain Res 2006;170:148–55. https://doi.org/10.1016/j.bbr.2006.02.010.
[197] Rasch B, Gais S, Born J. Impaired off-line consolidation of motor memories after combined blockade of cholinergic receptors during REM sleep-rich sleep. Neuropsychopharmacology 2009;34:1843–53. https://doi.org/10.1038/npp.2009.6.
[198] Hornung OP, Regen F, Danker-Hopfe H, Schredl M, Heuser I. The relationship between REM sleep and memory consolidation in old age and effects of cholinergic medication. Biol Psychiatry 2007;61:750–7. https://doi.org/10.1016/j.biopsych.2006.08.034.
*[199] Li W, Ma L, Yang G, Gan W-B. REM sleep selectively prunes and maintains new synapses in development and learning. Nat Neurosci 2017;20:427–37. https://doi.org/10.1038/nn.4479.
[200] Cordi MJ, Rasch B. How robust are sleep-mediated memory benefits? Curr Opin Neurobiol 2021;67:1–7. https://doi.org/10.1016/j.conb.2020.06.002.

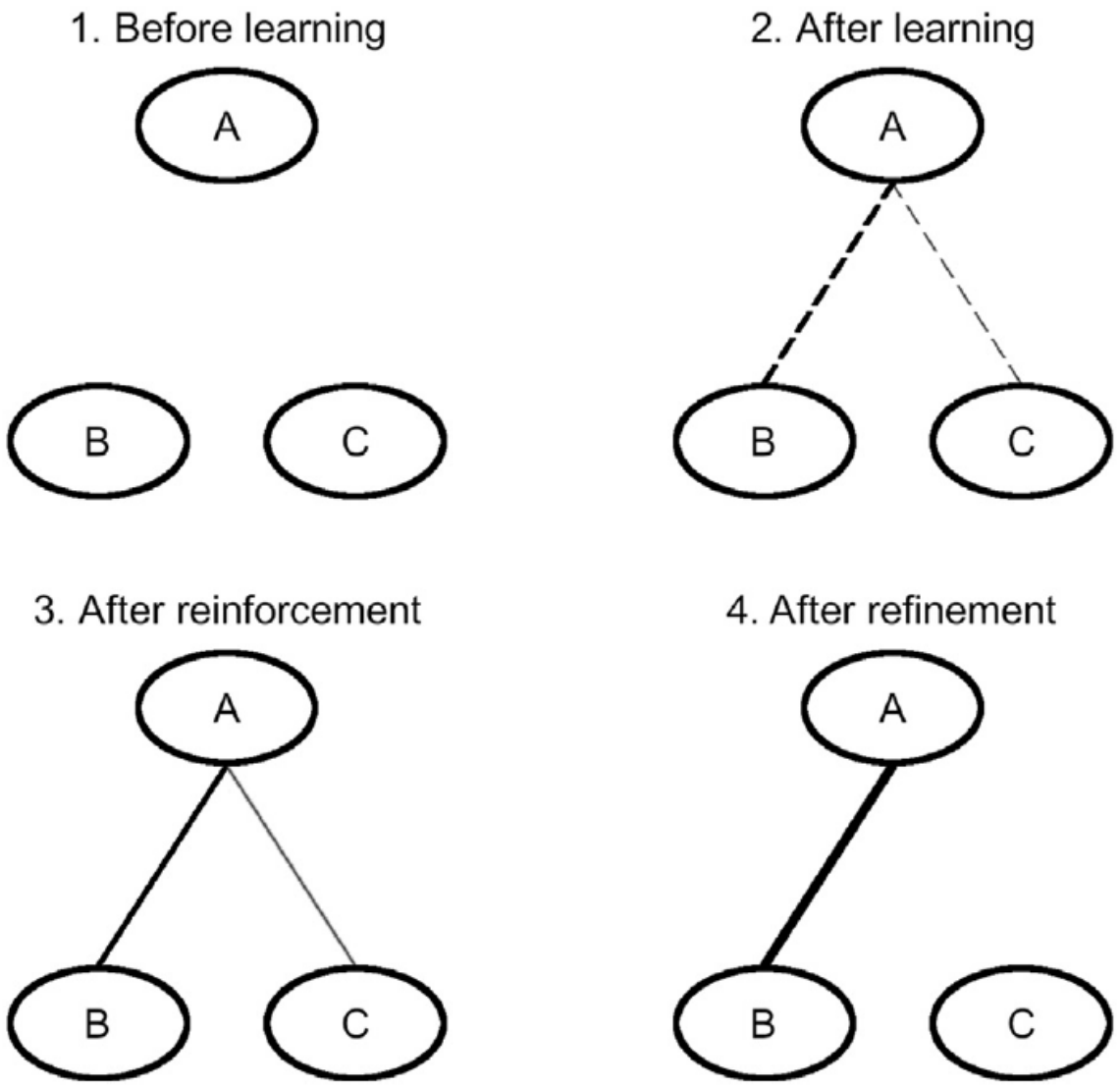

Figure 1. Depiction of the effects of learning, reinforcement, and refinement on the formation and processing of memories. In part 1, three components in the system that will hold the formed memories are identified as not connected before learning. In part 2, the dashed lines connecting A to B and A to C respectively indicate A-B and A-C memories acquired during learning. The darker line connecting A to B identifies the A-B memory as a more dominant memory relative to the A-C memory formed by the lighter dashed line. Both memories compete for retrieval, and each may be retrieved, but the dominant A-B memory would have a greater likelihood of retrieval. In step 3, it is shown that reinforcement has substantiated both the A-B and A-C memories, as indicated by the now solid connecting lines. In step 4, it is shown that refinement has selectively strengthened the dominant A-B memory, as indicated by the thickening of the connecting line, and weakened the A-C memory to the point of elimination. Retrievability of the A-B memory is ensured due to its substantiation in the system, and the A-B memory will be reliably retrieved due to the elimination of the competing A-C memory.