

Differential Effects of Non-REM and REM Sleep on Memory Consolidation?

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Abstract Sleep benefits memory consolidation. Previous theoretical accounts have proposed a differential role of slow-wave sleep (SWS), rapid-eye-movement (REM) sleep, and stage N2 sleep for different types of memories. For example the dual process hypothesis proposes that SWS is beneficial for declarative memories, whereas REM sleep is important for consolidation of non-declarative, procedural and emotional memories. In fact, numerous recent studies do provide further support for the crucial role of SWS (or non-REM sleep) in declarative memory consolidation. However, recent evidence for the benefit of REM sleep for non-declarative memories is rather scarce. In contrast, several recent studies have related consolidation of procedural memories (and some also emotional memories) to SWS (or non-REM sleep)-dependent consolidation processes. We will review this recent evidence, and propose future research questions to advance our understanding of the role of different sleep stages for memory consolidation.

Keywords Slow wave sleep · Rapid eye movement sleep · Declarative memory · Non-declarative memory · Emotional memory · Procedural memory · Memory consolidation · Reactivation

Introduction

Sleep benefits memories. Numerous studies convincingly show that newly acquired memories benefit from a consolidation period filled with sleep (reviewed in [1•]). While encoding and retrieval of memories takes place preferentially during waking, the active system consolidation hypothesis [1•, 2–4] assumes that sleep provides optimal conditions for an effective consolidation and stabilization of memories and their integration into long-term memory stores. Importantly, sleep is not uniform, but consists of highly different sleep stages: slow-wave sleep (SWS), which mainly occurs in the first half of the night (Fig. 1a), is characterized by slowly oscillating brain activity reflecting alternating periods of neural activity and neural silence (i.e., up and down states) that are highly synchronized over widespread cortical brain areas [5–7]; the lighter N2 non-rapid eye movement (REM) sleep is about equally present in the first and second halves of the night, and is marked by sleep spindles (i.e., distinct events of waxing and waning oscillatory activity in the 11–15 Hz range, occurring during both SWS and N2), as well as K-complexes (distinct occurrences of slow waves). SWS and N2 are only separated in human sleep recordings, but not in animal studies. In contrast, during REM sleep, occurring primarily in the second half of the night (Fig. 1a), the brain's oscillatory activity predominantly consists of mixed-frequency, low-amplitude oscillations resembling waking electroencephalographic activity combined with hippocampal theta oscillations, rapid-eye movements and reduced muscle tone [8, 9]. Owing to this paradoxical, rather wake-like, brain activity

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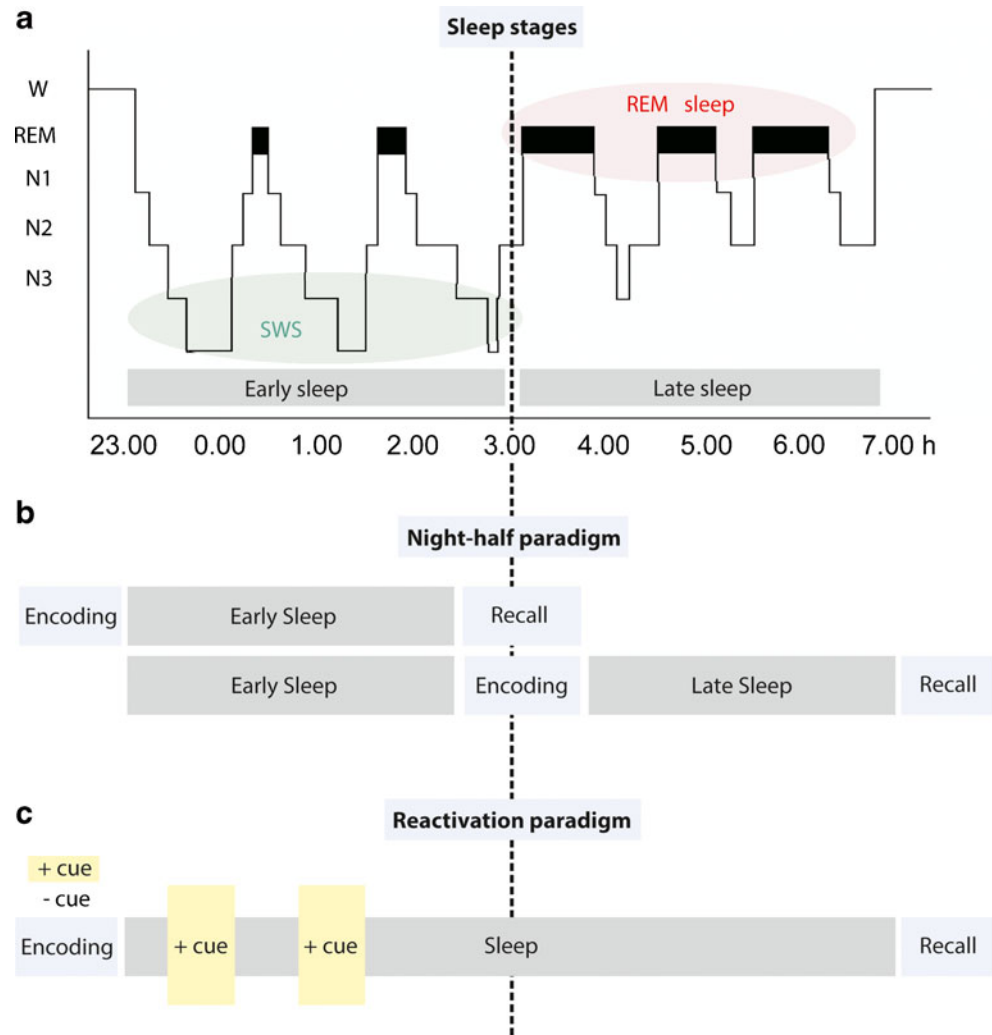
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Fig. 1 Human sleep pattern and paradigms used to investigate sleep stage-dependent memory consolidation during sleep. **(a)** Typical human sleep profile indicated in a hypnogram. While during early sleep slow-wave sleep (SWS) is prevailing, during late sleep rapid eye movement (REM) sleep predominates. Non-REM sleep encompasses SWS (N3) and N2, with approximately equal amounts of N2 sleep during early and late sleep. **(b)** Night-half paradigm. Participants either encode memories before (and recall after) a 3-h retention interval filled with early SWS-rich sleep (first night-half), or with late, REM-sleep-rich sleep. **(c)** Reactivation paradigm. Depicted is external reactivation during the first two cycles of SWS sleep. During encoding of a memory task, some stimuli are paired with a memory cue (e.g., odor or sound; + cue), while others are not (– cue). During post-learning sleep, the cue is presented again, typically during SWS, but other sleep stages would also be possible (e.g., early/late N2 sleep, REM sleep). Recall performance is tested after sleep and compared between cued and uncued stimuli



during REM sleep, most sleep and memory researchers in the last century (in particular, in rodent models) have focused on a critical role of REM sleep in memory processes (reviewed in [10]). Theories based mainly on human data hypothesized a differential role of sleep stages on memory (Table 1). One influential account is the so-called “dual process hypothesis”, which assumes that REM sleep benefits the consolidation of non-declarative memories (in particular, procedural skills and possibly also emotional memories; e.g., [11, 12]), whereas SWS is beneficial for hippocampus-dependent declarative memories of events (episodic memory) and facts (semantic memory) (e.g., [11]). Declarative memory encompasses explicit knowledge and can be consciously recalled. However, non-declarative memories as, for example, procedural memories are implicit and difficult to verbalize, and their initial encoding does not necessarily depend on the integrity of hippocampal structures [13]. Variations of the dual process hypothesis have also been proposed, associating different sleep stages (SWS, REM sleep, N2 sleep) to distinct memory

processes [14, 15]. Most recently, however, the focus of sleep and memory studies has almost exclusively shifted to SWS, implicating SWS either in global processes of synaptic down-scaling [16] or specific processes of reactivation, stabilization, and integration of memories (for reviews see [1••] and [17]), for both declarative memories [18, 19••] and non-declarative memory [20••, 21••, 22••]. Here, we aimed to review this recent evidence, evaluating whether recent findings in healthy humans still support the hypothesis of a differential role of REM, SWS, and N2 sleep for memory consolidation or not.

The Dual Process Hypothesis

The dual process hypothesis proposes that SWS preferentially benefits declarative memory, while REM sleep is of special importance for non-declarative memories [3, 10, 23]. Results in favor of the dual process hypothesis come mostly from studies using the night-half paradigm. In this paradigm

Table 1 Study paradigms, sleep stages, and effects on different types of memory consolidation in humans

Paradigm	Non-REM		REM
	S2	SWS	
Night-half paradigm	?	Declarative memory	Procedural memory Emotional memory
Selective sleep stage deprivation	Impairs simple motor tasks	No effects on declarative memory	Impairs complex memories (procedural + declarative?)
Oscillatory manipulation	?	Manipulating slow oscillations affects declarative memory	?
Pharmacological manipulation	Effects on declarative memory only when increasing both SWS and spindles		No effects of REM sleep suppression on procedural memory
Induced reactivation	Enhancement of declarative memory Enhancement of procedural memory Increase/decrease of emotional memory		?

(Fig. 1b), learning of a memory task is either followed by early (first night-half) or late sleep (second night-half) [24]. The first night-half is typically dominated by SWS, whereas the late night-half is dominated by REM sleep (Fig. 1a). The amount of N2 sleep is similar in both night-halves. Results from night-half studies have repeatedly shown that SWS predominantly benefits hippocampus-dependent declarative memory like learning of word lists, word-pairs, or spatial locations [11, 24–27]. In contrast, REM sleep is more important for procedural memories, including mirror tracing, priming, and implicit memory [11, 27–29]. Evidence from night-half paradigms also supports the notion that the emotional modulation of memories particularly benefits from late, REM sleep-rich sleep [12, 30, 31].

In addition to studies using the night-half paradigm, a differential role of sleep stages in memory consolidation is supported by numerous studies examining the effect of selective sleep stage deprivation on memory consolidation. As reviewed by Smith [10], these studies consistently show that selective REM sleep deprivation impairs the consolidation of cognitive procedural tasks like the tower of Hanoi task or word fragment completion, while the consolidation of “simple” declarative memories (words, word pairs, etc.) remains intact. However, more complex declarative memories like memory for prose, meaningless sentences, or stories were also affected by REM sleep deprivation, possibly containing some kind of “procedural” or emotional component. Furthermore, selective increases in REM sleep after learning have been particularly observed after learning of novel complex motor activity or other tasks containing a procedural component. Simple procedural memory tasks (i.e., pursuit rotor task) are mostly affected by selective deprivation of stage N2 sleep [32]. As most learning paradigms used in animal studies have a strong emotional component (i.e., fear conditioning, reward learning, etc.), the consistent evidence of REM sleep increases after learning or detrimental influences of

REM sleep deprivation might be taken as evidence in favor of a critical role of REM sleep in emotional memory processes (as reviewed in [33] and [34]).

In summary, evidence acquired until the beginning of this century supports the view of a differential role of sleep stages in distinct memory processes, relating SWS to (simple) declarative memories, REM sleep to (complex/cognitive) procedural and emotional memories, and N2 sleep/sleep spindles to simple motor tasks. In the following, we will review more recent evidence obtained in the last few years with respect to predictions of the extended dual process hypothesis.

Declarative Memory Consolidation

Declarative memory encompasses memory for events (episodic memory) and facts (semantic memory). Encoding, as well as initial retrieval, of declarative memories critically depend (refers to retrieval and encoding) on the integrity of the hippocampal formation [13]. The active system consolidation hypothesis assumes that the beneficial effect of sleep on declarative memory relies on a fine-tuned interaction between slow oscillatory activity during SWS, thalamo-cortical sleep spindles, and spontaneous hippocampal memory reactivations [2]. In accordance with this hypothesis, as well as the proposition of the dual process hypothesis, many recent human studies have confirmed the importance of SWS sleep for hippocampus-dependent declarative memory (see [1••], for a detailed review). For example, Alger et al. [35] showed that only a 60-min nap (containing SWS), but not a 10-min nap, shelters memory from future interference in a paired association task. The same result pattern was obtained when memory stability was tested 1 week later. Similarly, Diekelmann et al. [36••] found that the beneficial effect of sleep on memory stability in a two-dimensional object location task compared with wakefulness occurred only after a retention period filled

with 90 min of sleep, but not after 40 min of sleep. Furthermore, only in the 90-min sleep group was the amount of SWS positively correlated with memory performance. In another nap study, the nap-dependent benefit in the recognition of neutral pictures increased with an increasing delay between learning and nap onset (i.e., immediate, 2 h, and 4 h), probably owing to the increased amount of SWS in the delayed naps [37]. The importance of SWS for declarative memory consolidation is further supported by a recent study showing that slow wave activity (SWA; 0.5 – 4.5 Hz) during non-REM sleep (i.e., a marker of the depth of SWS) is associated both with age-related medial prefrontal cortex atrophy and impaired episodic long-term memory [38]. In striking contrast, Scullin [39] reported a negative correlation between the amount of SWS and memory for word pairs in older adults, whereas a positive correlation between declarative memory consolidation and SWS was only observed in younger adults. Similarly, in younger participants, SWA during non-REM sleep correlated positively with declarative memory consolidation of a word-list learning task and oscillatory power in the sleep spindle range [40]. In addition, the slow oscillation band and sleep spindle density have been related to integrating new memories into semantic memory [41, 42]. Finally, in preschool children, classroom naps improved memory for information learned during the morning classes only in habitual nappers, who probably sleep deeper during midday naps, and the nap-dependent improvement correlated with sleep spindle density [43].

Besides these mostly correlative results, the critical role for SWS for declarative memory consolidation is also supported by experimental findings. For example, induction of slow oscillations by electrical stimulation increased spontaneous slow oscillatory activity and improved declarative (but not procedural) memory consolidation across sleep ([44], although see [45] for a null finding in healthy elderly participants). In contrast, theta stimulation (typically associated with REM sleep) during REM sleep had no effect on declarative memory consolidation, whereas theta stimulation during non-REM sleep decreased sleep spindles and impaired declarative memory recall after sleep [46]. Experimental manipulation of slow oscillatory activity also increased new learning of declarative material after a nap [47], whereas suppressing SWA by administration of tones during sleep-impaired memory encoding and hippocampal functioning [48], supporting a role of SWS in preparatory processing for efficient learning the next day [49]. In a recent study, Ngo et al. [50] experimentally increased slow oscillations by presenting short tones in phase with the ongoing slow rhythmic occurrence of slow oscillations up-states. This specific “close-loop” auditory stimulation enhanced slow oscillatory activity, phase-coupled spindle activity, and declarative memory consolidation of word-pairs.

Signs of spontaneous hippocampal memory reactivation in rodents, as well as in humans, have been most consistently observed during SWS (for a review see [51]). The importance

of SWS for declarative memories is also elegantly supported by numerous recent studies experimentally inducing memory reactivation during sleep (see Fig. 1c for an example of the reactivation procedure). Thus, most studies inducing memory reactivations during sleep by re-exposure to learning-associated memory cues (e.g., odors, sounds) successfully administered these cues mostly exclusively during SWS, thereby improving memory recall the next day [18, 19••, 52••, 53]. In contrast, odor-induced memory reactivations during REM sleep had no effect on declarative memory consolidation [18]. Odor-induced memory reactivation during SWS stabilized memories against future interference even in the absence of subsequent REM sleep [54••], suggesting that a complete SWS–REM cycle is not necessary for the stabilization of memories by reactivation. A recent study additionally shows that odor-induced reactivation of declarative memories is associated with an increase in parietal fast spindle power, as well as an increased slope of slow oscillations (Rihm et al., submitted), adding further support to the hypothesis of a fine-tuned interaction between slow oscillations, fast spindles, and memory reactivation for successful declarative memory consolidation during sleep.

In sum, the critical role for SWS, as well as its characteristic components (slow oscillations/SWA, as well as sleep spindles), is strongly supported by recent findings. However, it still remains an open question whether declarative memory processes are solely acting during SWS or whether they similarly extend to sleep stage N2. Numerous studies have consistently implicated sleep spindles in declarative memory processes, (see [55] for a review). In support of a specific role of sleep spindles during SWS for memory, Cox et al. [56] reported that sleep spindle density only predicted declarative memory consolidation when measured during SWS, but not during stage N2 sleep. In contrast, in naps containing only N2 sleep, consolidation of an associative learning task was also positively related to oscillatory activity in the slow delta and sleep spindles range [57], suggesting a quantitative rather than a qualitative distinction between SWS and N2 for declarative memory consolidation during sleep. In support of this latter view, pharmacologically increasing sleep spindles, as well as SWS, by administration of a short-acting gamma aminobutyric acid-A agonist (zolpidem) improved verbal memory consolidation, whereas solely pharmacological increasing SWS did not [58, 59]. Unfortunately, studies experimentally inducing memory reactivations during N2 sleep are still missing. Future studies should experimentally induce memory reactivations selectively during N2 sleep or SWS to further clarify the relative importance of N2 sleep versus SWS for declarative memory consolidation.

Procedural Memories

Procedural memories are often also referred to as skill memories. Typical procedural memory tasks used in sleep and memory research are finger-sequence tapping, mirror tracing,

or other forms of visuo-motor learning. In contrast to declarative memories, acquisition of procedural memory does not necessarily require an intact hippocampal formation, although interactions between the hippocampus and brain areas involved in skill learning (e.g., striatal areas, motor cortex) are likely [60]. Similarly, a complex learning task might often involve both procedural and declarative learning components (e.g., complex motor movements, language learning; see [61]).

According to the dual process theory, consolidation of procedural memory tasks critically depends on REM sleep [10, 11]. However, only very few recent human studies support this claim. For example, Fischer et al. [62] reported that sleep-dependent performance enhancements in the finger-sequence tapping task significantly correlates with the time spent in REM sleep, although this result could not be replicated in a subsequent functional magnetic resonance imaging study [63]. In addition, one study showed that suppression of REM sleep by blocking nicotinic and muscarinic cholinergic receptors impaired consolidation of the finger-sequence tapping task [64]. However, REM sleep suppression by pharmacologically increasing serotonergic or noradrenergic tone by administration of antidepressants did not impair procedural memory consolidation, but rather enhanced performance in a finger-sequence tapping task [65]. Moreover, the benefits in performance after pharmacological REM sleep suppression were associated with increases in spindle density. This finding fits well with the clinical observation that REM sleep suppression over longer time periods (e.g., during antidepressant therapy) does not impair memory for motor skills [66, 67]. Taken together, these studies suggest the possibility that the cholinergic tone during late REM sleep-rich sleep (including both REM and N2 sleep), but not REM sleep per se, is necessary for successful procedural memory consolidation.

In fact, several recent findings support the notion that the consolidation of procedural memories depends on non-REM sleep rather than REM sleep, particularly implicating sleep spindles, N2 sleep, and SWA in this process. Several studies have consistently reported positive correlations between sleep-dependent performance enhancements in the finger-sequence tapping task with the amount of N2 sleep or sleep spindles during non-REM sleep [68, 69]. Furthermore, sleep spindles are increased during sleep after the performance of simple motor tasks [70]. In addition, acquisition of a rotor adaptation task resulted in a local increase of SWA in brain areas involved in procedural motor learning, and these local increases in SWA were positively correlated with overnight improvements in motor skills [71]. Conversely, arm immobilization resulted in a local decrease in SWA during subsequent non-REM sleep [72]. Evidence for a causal role of SWA in procedural memory consolidation is provided by studies showing that suppressing SWA using tones diminished overnight improvements in a texture discrimination task [73] or a visuomotor task [74••]. Electrical stimulation of oscillatory

activity remains inconclusive; both slow oscillatory stimulation during non-REM sleep and theta stimulation during REM sleep (as well as theta stimulation during non-REM sleep) did not affect procedural memory consolidation [44, 46].

Most interestingly, two recent reactivation studies also support a role of non-REM sleep rather than REM sleep for procedural memory consolidation. In both studies, participants learned to play melodies before sleep. During subsequent SWS or early sleep, participants were repeatedly re-exposed to parts of the learned melodies, which resulted in specific performance benefits for the melodies cued during SWS or early, SWS-rich sleep [20••, 21••]. Unfortunately, cueing of melodies during REM sleep was not tested in these studies. A first hint that reactivation of procedural memories during REM sleep might be ineffective is provided by the finding that odor-induced memory reactivation during REM sleep does not improve consolidation of a finger-sequence tapping task [18], although further studies are needed to further evaluate this finding.

Thus, in spite of evidence supporting a critical role of REM sleep for procedural memories (arising particularly from selective REM sleep deprivation procedures or studies using the night half paradigm), recent human studies support a critical role of non-REM sleep, sleep spindles, and SWA in the consolidation of skills. It has been argued that selective REM sleep deprivation procedures might be confounded by induced stress during late-night sleep [75]. Furthermore, procedural memory benefits observed after late sleep in the night-half paradigm might be related to differences in early- versus late-night N2 sleep instead of REM sleep (see [1••]). However, it might be argued that the recent support for a role of non-REM sleep in procedural memory consolidation is due to declarative components or hippocampal contributions to the procedural learning tasks examined in sleep and memory research [60, 76]. Future studies are required to test whether skill-learning actually depends on non-REM sleep, and whether these processes share similar mechanisms (e.g., reactivation, cross-frequency synchronization, system consolidation, etc.) as underlying the consolidation of declarative memories during non-REM sleep.

Emotional Memories

Emotional events are better remembered than neutral ones. It is widely assumed that the emotional memory enhancements are due to modulatory influences of the amygdala on hippocampal memory-encoding processes [77]. Several studies suggest that emotional memories benefit more from sleep than neutral memories (e.g., [12, 78], for a review see [79]). This benefit is even detectable after several years [80]. As most learning tasks used in rodents have a strong emotional component (e.g., aversive/appetitive conditioning, reward learning, etc.), the consistent implication of REM sleep in memory processes in rodents might be taken as support for a critical role of REM sleep for emotional memories (for a review see, e.g., [81]).

In addition, early consideration of the role of vivid dreams in emotional reprocessing in humans [82], increases in amygdala activation during REM sleep [83], and the typical changes in REM sleep observed in mood disorders [84] have been taken as evidence for emotional reprocessing during REM sleep. Recently, Walker [85] has proposed that REM sleep is implicated in two ways in emotional memory reprocessing: while the content of the emotional memory is strengthened, the affective tone associated with the memory is weakened during REM sleep (“sleep to forget and sleep to remember” [SFSR] model [86•]). Recent human studies have largely supported the notion of an important role of REM sleep for emotional memory reprocessing, although some conflicting results are reported.

Consistent with previous findings from a night-half paradigm study [30], Groch et al. [31] recently showed that late, REM sleep-rich sleep (but not early SWS-rich sleep) particularly benefits memory for emotional compared with neutral pictures. These benefits were associated with a late positive potential over frontal brain regions as measured by event-related potentials. In addition, Nishida et al. [87] reported that recognition of emotional versus neutral pictures is particularly associated with the amount of REM sleep, as well as oscillatory theta activity during REM sleep. In another study [88], conditioned fear and underlying amygdala activation were increased after a retention interval filled with sleep compared with wakefulness, and the sleep-related increases in anxiety (as measured by skin conductance response) was positively correlated with REM sleep. In support of the SFSR hypothesis, van der Helm et al. [89] showed that amygdala activity during viewing of emotional pictures was attenuated after sleep when these pictures had already been seen before sleep. Importantly, the decrease in amygdala activation was associated with oscillatory gamma activity (> 30 Hz) during intervening REM sleep. Furthermore, in a different study, only participants whose naps contained REM sleep managed to reduce emotional reactivity to anger and fear pictures in a face recognition task [90]. However, other studies do not support the notion of a reduction of memory-associated emotional reactivity [31, 91, 92].

While most of the studies reviewed above support a specific role of REM sleep for emotional memory reprocessing, some recent studies also implicate non-REM sleep in the consolidation of emotional memories. For example, blocking release of norepinephrine during SWS diminishes the emotional memory effect of better recall of the temporal content of an emotional story compared with a neutral story [93]. In addition, pharmacologically increasing sleep spindles and SWS specifically improved recall of negative stimuli, whereas increasing only SWS did not influence emotional memory consolidation during sleep [94]. Furthermore, a recent study using odor-induced memory reactivation of fear memories reported that cueing fear memories during SWS induced an extinction of these emotional memories, together with its neural responses in the amygdala [22•]. Unfortunately, the effect of cueing during REM sleep was not

tested in this study. Similarly, low-value memory items could be rescued by cueing during non-REM sleep, diminishing the influence of reward on memory [53]. Interestingly, previous rodents studies using cueing of fear memories during non-REM sleep similarly observed a decrease in fear response after cueing during sleep [95], whereas cueing during REM sleep increased fear responses ([96]; see [81] for a review). In striking contrast to these results, a very recent study reported an increase in fear response after cueing of fear memories during SWS in rodents; this increase in fear was dependent on protein synthesis during sleep [97•]. Thus, in view of these inconsistent results, further reactivation studies are required to specifically examine the possible sleep stage dependency of strengthening or weakening emotional memories during sleep.

Conclusion

Given the results from recent studies, it appears that assumptions of the dual process hypothesis that SWS sleep benefits declarative memory, while REM sleep benefits non-declarative memory, are too much of a simplification to explain the diverse data on sleep and memory (see also [98]). While the crucial role of SWS (but also N2 sleep) for declarative memories is well supported, procedural memory also appears to be dependent on non-REM sleep (particularly sleep spindles), rather than REM sleep. Furthermore, while a role of REM sleep in emotional memory processing is more likely, at least some aspects of emotional memory consolidation occur also during non-REM sleep. Taken together, processing of several different types of memories might actually depend on consolidation processes occurring during non-REM sleep (i.e., SWS and N2 sleep), while the exact role of REM sleep in memory becomes more and more obscure. Future research is needed to answer the question of whether the effects of non-REM sleep and REM sleep on memory consolidation are, indeed, differential or not.

Thus, one of the most important questions for the field of sleep and memory research will be to define (or redefine) the role of REM sleep in memory processing. Does REM sleep particularly benefit emotional reprocessing and what are the underlying mechanisms? Does emotional reprocessing during REM sleep also depend on spontaneous memory reactivation processes and is there any relation with vivid dreaming? Can memories be (externally) reactivated during REM sleep, and what are the consequences for the strength of the memory content and its associated emotion? Or does REM sleep after non-REM sleep play a sequential role in memory processes, as suggested previously [2, 99], and what exactly are the underlying mechanisms and effects on memory consolidation?

Future sleep and memory studies need to define more clearly the mechanisms underlying procedural memory consolidation during sleep. Does procedural memory consolidation only benefit from non-REM sleep and induced reactivation when it

involves declarative/hippocampal components? Or does pure skill-learning (possibly in patients with hippocampal lesions) also profit from reactivating procedural memories during SWS? What exactly is the functional role of sleep spindles for procedural memory consolidation?

With regard to declarative memory consolidation, a more careful examination of the contributions of SWS and N2 sleep is required. To test this question, reactivation studies should compare the benefits of inducing memory reactivations solely during N2 or SWS. In addition, the possibly specific role of N2 sleep in the first and the second half of the night for memory consolidation should be investigated. In addition, factors already relevant during the encoding of memories might be highly relevant for determining the type of consolidation during sleep, possibly also with respect to the contribution of different sleep stages (see [100] for a review). For example, sleep specifically benefits memories that are of future relevance [101–103], and only participants who expected the later recall showed an increase in deep stage 4 sleep [103]. In addition, prospective memory (i.e., memorizing to perform an action in the future) was better after an initial period of SWS as compared to an initial period of REM sleep [104]. Thus, the exact role of performance level, future relevance, the existence of prior knowledge and schemes, and the depth of encoding and degree of hippocampal involvement at learning [101] should be further examined and specifically related to the SWS, N2, or non-REM dependent processes of declarative memory consolidation and its underlying mechanisms acting during sleep.

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References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

- 1.•• Rasch B, Born J. About sleep's role in memory. *Physiol Rev*. 2013;93:681–766. *A comprehensive review on the current status of sleep and memory research.*

2. Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci*. 2010;11:114–26.
3. Marshall L, Born J. The contribution of sleep to hippocampus-dependent memory consolidation. *Trends Cogn Sci*. 2007;11:442–50.
4. Born J, Wilhelm I. System consolidation of memory during sleep. *Psychol Res*. 2012;76:192–203.
5. Mölle M, Marshall L, Gais S, Born J. Learning increases human electroencephalographic coherence during subsequent slow sleep oscillations. *Proc Natl Acad Sci U S A*. 2004;101:13963–8.
6. Menicucci D, Piarulli A, DeBarnot U, d'Ascanio P, Landi A, Gemignani A. Functional structure of spontaneous sleep slow oscillation activity in humans. *PLoS One*. 2009;4:e7601.
7. Mölle M, Born J. Slow oscillations orchestrating fast oscillations and memory consolidation. *Prog Brain Res*. 2011;193:93–110.
8. Cantero JL, Atienza M, Stickgold R, Kahana MJ, Madsen JR, Kocsis B. Sleep-dependent theta oscillations in the human hippocampus and neocortex. *J Neurosci*. 2003;23:10897–903.
9. Buzsáki G. Theta oscillations in the hippocampus. *Neuron*. 2002;33:325–40.
10. Smith CT. Sleep states and memory processes in humans: procedural versus declarative memory systems. *Sleep Med Rev*. 2001;5:491–506.
11. Plihal W, Born J. Effects of early and late nocturnal sleep on declarative and procedural memory. *J Cogn Neurosci*. 1997;9:534–47.
12. 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.
13. Squire LR. Memory systems of the brain: A brief history and current perspective. *Neurobiol Learn Mem*. 2004;82:171–7.
14. Rauchs G, Desgranges B, Foret J, Eustache F. The relationships between memory systems and sleep stages. *J Sleep Res*. 2005;14:123–40.
15. Walker MP, Stickgold R. Sleep-dependent learning and memory consolidation. *Neuron*. 2004;44:121–33.
16. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev*. 2006;10:49–62.
17. Oudiette D, Paller K A. Upgrading the sleeping brain with targeted memory reactivation. *Trends Cogn Sci*. 2013;1–8.
18. Rasch B, Buchel C, Gais S, Born J. Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science*. 2007;315:1426–9.
- 19.•• Rudoy JD, Voss JL, Westerberg CE, Paller KA. Strengthening individual memories by reactivating them during sleep. *Science*. 2009;326:1079. *The authors show that reactivation can selectively enhance memory consolidation. Spatial locations of items in an object-location task that are cued (sound) during a post-learning nap are less often forgotten than locations of uncued items.*
- 20.•• Schönauer M, Geisler T, Gais S. Strengthening procedural memories by reactivation in sleep. *J Cogn Neurosci*. 2013;1–11. *The study shows that auditory reactivation during early sleep strengthens procedural memory consolidation (finger-tapping task) during sleep, but not during wakefulness. The benefit is selective for cued sequences.*
- 21.•• 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. *Auditory reactivation of procedural memory during SWS of an afternoon nap improved accuracy in after sleep memory performance showing a role of SWS for consolidation of procedural memory.*
- 22.•• Hauner KK, Howard JD, Zelano C, Gottfried JA. Stimulus-specific enhancement of fear extinction during slow-wave sleep. *Nat Neurosci*. 2013;16:1553–5. *The authors show that in humans, memories that are reactivated during SWS elicit a smaller fear*

- response when cues are again presented during wake (smaller skin conductance response). This study is in contrast with a recent study in mice showing that consolidation of fear memories during sleep is strengthened* [97].
23. Gais S, Born J. Declarative memory consolidation: mechanisms acting during human sleep. *Learn Mem.* 2004;11:679–85.
 24. 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;88:361–6.
 25. Fowler MJ, Sullivan MJ, Ekstrand BR. Sleep and memory. *Science.* 1973;179.
 26. Barrett TR, Ekstrand BR. Effect of sleep on memory: III. Controlling for time-of-day effects. *J Exp Psychol.* 1972;96:321–7.
 27. Plihal W, Born J. Effects of early and late nocturnal sleep on priming and spatial memory. *Psychophysiology.* 1999;36:571–82.
 28. Verleger R, Schuknecht S-V, Jaśkowski P, Wagner U. Changes in processing of masked stimuli across early- and late-night sleep: a study on behavior and brain potentials. *Brain Cogn.* 2008;68:180–92.
 29. Wagner U, Hallschmid M, Verleger R, Born J. Signs of REM sleep dependent enhancement of implicit face memory: a repetition priming study. *Biol Psychol.* 2002;62.
 30. Wagner U, Fischer S, Born J. Changes in emotional responses to aversive pictures across periods rich in slow-wave sleep versus rapid eye movement sleep. *Psychosom Med.* 2002;64:627–34.
 31. Groch S, Wilhelm I, Diekelmann S, Born J. The role of REM sleep in the processing of emotional memories: evidence from behavior and event-related potentials. *Neurobiol Learn Mem.* 2013;99:1–9.
 32. Smith CT, MacNeill C. Impaired motor memory for a pursuit rotor task following Stage 2 sleep loss in college students. *J Sleep Res.* 1994;3:206–13.
 33. Smith CT. Sleep states, memory processes and synaptic plasticity. *Behav Brain Res.* 1996;78:49–56.
 34. Smith CT. Sleep states and memory processes. *Behav Brain Res.* 1995;69:137–45.
 35. Alger SE, Lau H, Fishbein W. Slow wave sleep during a daytime nap is necessary for protection from subsequent interference and long-term retention. *Neurobiol Learn Mem.* 2012;98:188–96.
 36. 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. *This study shows that reactivation can boost the beneficial effect of sleep on memory consolidation. While a 40-min nap without reactivation does not benefit memory as compared to wakefulness, a nap of 40 minutes with reactivation led to the same consolidation benefit as a 90-min nap without reactivation. External reactivation leads to faster consolidation and may compensate for less SWS.*
 37. Alger SE, Lau H, Fishbein W. Delayed onset of a daytime nap facilitates retention of declarative memory. *PLoS One.* 2010;5:e12131.
 38. Mander BA, Rao V, Lu B, Saletin JM, Lindquist JR, Ancoli-Israel S, et al. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nat Neurosci.* 2013;1–10.
 39. Scullin MK. Sleep, memory, and aging: the link between slow-wave sleep and episodic memory changes from younger to older adults. *Psychol Aging.* 2013;28:105–14.
 40. Piosczyk H, Holz J, Feige B, Spiegelhalder K, Weber F, Landmann N, et al. The effect of sleep-specific brain activity versus reduced stimulus interference on declarative memory consolidation. *J Sleep Res.* 2013;22:406–13.
 41. Tamminen J, Payne JD, Stickgold R, Wamsley EJ, Gaskell MG. Sleep spindle activity is associated with the integration of new memories and existing knowledge. *J Neurosci.* 2010;30:14356–60.
 42. Tamminen J, Lambon Ralph MA, Lewis PA. The role of sleep spindles and slow-wave activity in integrating new information in semantic memory. *J Neurosci.* 2013;33:15376–81.
 43. Kurdziel L, Duclos K, Spencer RMC. Sleep spindles in midday naps enhance learning in preschool children. *Proc Natl Acad Sci U S A.* 2013;110:17627–72.
 44. Marshall L, Helgadottir H, Mölle M, Born J. Boosting slow oscillations during sleep potentiates memory. *Nature.* 2006;444:610–3.
 45. Eggert T, Dorn H, Sauter C, Nitsche MA, Bajbouj M, Danker-Hopfe H. No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory consolidation in healthy elderly subjects. *Brain Stimul.* 2013;6:938–45.
 46. Marshall L, Kirov R, Brade J, Mölle M, Born J. Transcranial electrical currents to probe EEG brain rhythms and memory consolidation during sleep in humans. *PLoS One.* 2011;6:e16905.
 47. Antonenko D, Diekelmann S, Olsen C, Born J, Mölle M. Napping to renew learning capacity: enhanced encoding after stimulation of sleep slow oscillations. *Eur J Neurosci.* 2013;37:1142–51.
 48. Van Der Werf YD, Altena E, Schoonheim MM, Sanz-Arigita EJ, Vis JC, De Rijke W, et al. Sleep benefits subsequent hippocampal functioning. *Nat Neurosci.* 2009;12:122–3.
 49. Van Der Werf YD, Altena E, Vis JC, Koene T, Van Someren EJW. Reduction of nocturnal slow-wave activity affects daytime vigilance lapses and memory encoding but not reaction time or implicit learning. *Prog Brain Res.* 2011;193:245–55.
 50. 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.
 51. O'Neill J, Pleydell-Bouverie B, Dupret D, Csicsvari J. Play it again: reactivation of waking experience and memory. *Trends Neurosci.* 2010;33:220–9.
 52. Fuentemilla L, Miró J, Ripollés P, Vilà-Balló A, Juncadella M, Castañer S, et al. Hippocampus-dependent strengthening of targeted memories via reactivation during sleep in humans. *Curr Biol.* 2013;23:1769–75. *This study shows that hippocampal activity is crucial for beneficial effects of reactivation on memory consolidation. The authors compared effects of external reactivation cues (sounds) during SWS on memory consolidation in healthy individuals and epileptic patients with unilateral and bilateral hippocampal sclerosis. External reactivation during sleep only benefited memory in healthy individuals and epileptic patients with unilateral hippocampal sclerosis.*
 53. 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.
 54. 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. *The authors investigated differential effects of reactivation during waking and sleep. Interestingly, reactivation of memory during wake leads to destabilization of memory while reactivation of memory during sleep leads to stabilization of memory. Moreover, REM sleep does not seem to be necessary for stabilization of memory, as also reactivation during a period of SWS sleep not containing REM sleep leads to stabilization of memory.*
 55. Lüthi A. Sleep spindles: where they come from, what they do. *Neuroscientist.* 2013 Aug 27 [Epub ahead of print].

56. Cox R, Hofman WF, Talamini LM. Involvement of spindles in memory consolidation is slow wave sleep-specific. *Learn Mem.* 2012;19:264–7.
57. Ruch S, Marques 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.
58. Mednick SC, McDevitt EA, Walsh JK, Wamsley E, Paulus M, Kanady JC, et al. The critical role of sleep spindles in hippocampal-dependent memory: a pharmacology study. *J Neurosci.* 2013;33:4494–504.
59. Feld GB, Wilhelm I, Ma Y, Groch S, Binkofski F, Mölle M, et al. Slow wave sleep induced by GABA agonist tiagabine fails to benefit memory consolidation. *Sleep.* 2013;36:1317–26.
60. Albouy G, King BR, Maquet P, Doyon J. Hippocampus and striatum: Dynamics and interaction during acquisition and sleep-related motor sequence memory consolidation. *Hippocampus.* 2013;23:985–1004.
61. Peigneux P, Laureys S, Delbeuck X, Maquet P. Sleeping brain, learning brain. The role of sleep for memory systems. *Neuroreport.* 2001;12:A111–24.
62. Fischer S, Hallschmid M, Elsner AL, Born J. Sleep forms memory for finger skills. *Proc Natl Acad Sci U S A.* 2002;99:11987–91.
63. Fischer S, Nitschke MF, Melchert UH, Erdmann C, Born J. Motor memory consolidation in sleep shapes more effective neuronal representations. *J Neurosci.* 2005;25:11248–55.
64. 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.
65. 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.
66. Siegel JM. The REM, sleep-memory consolidation hypothesis. *Science.* 2001;294:1058–63.
67. Vertes RP, Eastman KE. The case against memory consolidation in REM sleep. *Behav Brain Sci.* 2000;23:867–76.
68. 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.
69. Nishida M, Walker MP. Daytime naps, motor memory consolidation and regionally specific sleep spindles. *PLoS One.* 2007;2:e341.
70. Fogel SM, Smith CT, Cote KA. Dissociable learning-dependent changes in REM and non-REM sleep in declarative and procedural memory systems. *Behav Brain Res.* 2007;180:48–61.
71. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. *Nature.* 2004;430:78–81.
72. 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;9:1169–76.
73. Aeschbach D, Cutler AJ, Ronda JM. A role for non-rapid-eye-movement sleep homeostasis in perceptual learning. *J Neurosci.* 2008;28:2766–72.
74. 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;32:1273–84. *Acoustic suppression of slow wave activity diminished overnight improvement in a visuomotor learning task as compared to a control group. These results demonstrate the importance of slow wave activity for the formation of procedural memory.*
75. Born J, Gais S. REM sleep deprivation: The wrong paradigm leading to wrong conclusions. *Behav Brain Sci.* 2000;23:912–3.
76. Albouy G, Sterpenich V, Vandewalle G, Darsaud A, Gais S, Rauchs G, et al. Interaction between hippocampal and striatal systems predicts subsequent consolidation of motor sequence memory. *PLoS One.* 2013;8:e59490.
77. McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu Rev Neurosci.* 2004;27:1–28.
78. Hu P, Stylos-Allan M, Walker MP. Sleep facilitates consolidation of emotional declarative memory. *Psychol Sci.* 2006;17:891–8.
79. Payne JD, Kensinger EA. Sleep's role in the consolidation of emotional episodic memories. *Curr Dir Psychol Sci.* 2010;19:290–5.
80. Wagner U, Hallschmid M, Rasch B, Born J. Brief sleep after learning keeps emotional memories alive for years. *Biol Psychiatry.* 2006;60:788–90.
81. Hennevin E, Huetz C, Edeline J-M. Neural representations during sleep: from sensory processing to memory traces. *Neurobiol Learn Mem.* 2007;87:416–40.
82. Freud S. The interpretation of dreams. 1900.
83. Hobson JA, Pace-Schott EF. The cognitive neuroscience of sleep: neuronal systems, consciousness and learning. *Nat Rev Neurosci.* 2002;3:679–93.
84. Tsuno N, Besset A, Ritchie K. Sleep and depression. *J Clin Psychiatry.* 2005;66:1254–69.
85. Walker MP. The role of sleep in cognition and emotion. *Ann N Y Acad Sci.* 2009;1156:168–97.
86. Walker MP, van der Helm E. Overnight therapy? The role of sleep in emotional brain processing. *Psychol Bull.* 2009;135:731–48. *An important review proposing that a role of sleep for emotional memory processing is twofold: while the emotional context is strengthened by sleep, the associated emotion of the memory is reduced.*
87. Nishida M, Pearsall J, Buckner RL, Walker MP. REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cereb Cortex.* 2009;19:1158–66.
88. Menz MM, Rihm JS, Salari N, Born J, Kalisch R, Pape HCC, et al. The role of sleep and sleep deprivation in consolidating fear memories. *Neuroimage.* 2013;75:87–96.
89. Van der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP. REM sleep depotentiates amygdala activity to previous emotional experiences. *Curr Biol.* 2011;21:2029–32.
90. Gujar N, McDonald SA, Nishida M, Walker MP. A role for REM sleep in recalibrating the sensitivity of the human brain to specific emotions. *Cereb Cortex.* 2011;21:115–23.
91. Baran B, Pace-Schott EF, Ericson C, Spencer RM. Processing of emotional reactivity and emotional memory over sleep. *J Neurosci.* 2012;32:1035–42.
92. Deliens G, Neu D, Peigneux P. Rapid eye movement sleep does not seem to unbind memories from their emotional context. *J Sleep Res.* 2013;36:1875–83.
93. Groch S, Wilhelm I, Diekelmann S, Sayk F, Gais S, Born J. Contribution of norepinephrine to emotional memory consolidation during sleep. *Psychoneuroendocrinology.* 2011;36:1342–50.
94. Kaestner EJ, Wixted JT, Mednick SC. Pharmacologically increasing sleep spindles enhances recognition for negative and high-arousal memories. *J Cogn Neurosci* 2013;1597–610.
95. Hars B, Hennevin E. Impairment of learning by cueing during postlearning slow-wave sleep in rats. *Neurosci Lett.* 1987;79:290–4.

96. Hennevin E, Hars B. Is increase in post-learning paradoxical sleep modified by cueing? *Behav Brain Res.* 1987;24:243–9.
- 97.●● Rolls A, Makam M, Kroeger D, Colas D, de Lecea L, Heller HC. Sleep to forget: interference of fear memories during sleep. *Mol Psychiatry.* 2013;18:1166–70. *Reactivating fear memories during non-REM sleep in mice using an odor conditioning paradigm, leads to stronger consolidation of fear memories during sleep. This effect depends on protein synthesis in the basolateral amygdala. These results are in contrast with a study of fear consolidation during sleep in humans [21].*
98. Stickgold R. Parsing the role of sleep in memory processing. *Curr Opin Neurobiol.* 2013;23:847–53.
99. Ficca G, Salzarulo P. What in sleep is for memory. *Sleep Med.* 2004;5:225–30.
100. Stickgold R, Walker MP. Sleep-dependent memory triage: evolving generalization through selective processing. *Nat Neurosci.* 2013;16:139–45.
101. Rauchs G, Feyers D, Landeau B, Bastin C, Luxen A, Maquet P, et al. Sleep contributes to the strengthening of some memories over others, depending on hippocampal activity at learning. *J Neurosci.* 2011;31:2563–8.
102. Saletin JM, Goldstein AN, Walker MP. The role of sleep in directed forgetting and remembering of human memories. *Cereb Cortex.* 2011;21:2534–41.
103. Wilhelm I, Diekelmann S, Molzow I, Ayoub A, Mo M, Born J. Sleep selectively enhances memory expected to be of future relevance. *J Neurosci.* 2011;31:1563–9.
104. Diekelmann S, Wilhelm I, Wagner U, Born J. Sleep to implement an intention. *Sleep.* 2013;36:149–53.