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# The differing roles of NREM and REM sleep in the slow enhancement of skills and schemas

Sofia Isabel Ribeiro Pereira<sup>1</sup>, Penelope Lewis<sup>1</sup>

<sup>1</sup>School of Psychology, Cardiff University Brain Research Imaging Centre, Cardiff, Wales, CF24-4HQ, UK

**Corresponding author:** Penelope Lewis ([lewisp8@cardiff.ac.uk](mailto:lewisp8@cardiff.ac.uk)), Cardiff University Brain Research Imaging Centre, Maindy Rd, Cardiff, CF24 4HQ, United Kingdom

## Abstract

Sleep's effect on memory may not become evident for several days or weeks after learning, especially for motor skills and schema-related learning. Here, we propose a potential mechanism which may be underlying the slow enhancement of skills and schemas by examining the biological events which take place during NREM and REM sleep. We suggest that the immediate benefits of sleep are mainly due to reactivation during NREM sleep, while the delayed effects are mainly due to plasticity-related changes occurring at the molecular, cellular and system levels, and which require long periods of time to occur. There is increasing evidence that these events may take place preferentially during REM sleep, thus shedding further light on the function of this sleep stage.

**Keywords:** sleep; NREM; REM; skills; schemas; plasticity; myelin.

## Highlights

- Reactivation in NREM facilitates capture of plasticity-related products into synapses;
- Reactivated dendritic spines undergo remodelling during REM sleep;
- Sleep facilitates myelination, memory corticalization and reorganization;
- These slowly evolving processes may be important for motor skills and schemas.

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## 34 **Introduction**

35 It is well established that sleep plays an important role in memory consolidation (see [1] for a review).  
36 While great emphasis has been placed on the relationship between NREM sleep specifically and  
37 memory (see [2] for a review), REM sleep's contribution continues to be largely neglected.  
38 Furthermore, an increasing body of evidence suggests that some forms of sleep-dependent memory  
39 consolidation might require extended periods of time to unfold and emerge as quantifiable changes  
40 in behaviour, particularly motor skills [3] and schemas [4] (see Box 1 for more details).  
41 Recently, a new model integrating NREM and REM functions in synaptic plasticity has been proposed  
42 [5] (see steps 1 and 2 below for more details). In parallel, REM sleep has been implicated in myelination  
43 [6] and memory corticalization [7]. Here, we integrate these findings in an attempt to explain the  
44 mechanism underlying the slowly evolving consolidation of memories, particularly motor skills and  
45 schemas. We examine the complementary contributions of NREM and REM sleep in molecular, cellular  
46 and systems consolidation and shed further light on REM sleep's function.

47

### 48 **Box 1. Sleep-related enhancement of skills and schemas unfolds gradually over time**

49 A widely accepted model of motor skill consolidation suggests that procedural memories undergo two  
50 stages of consolidation: an initial process of stabilization, which does not necessarily require sleep,  
51 and a late process of sleep-dependent enhancement, which can take several days or even weeks [8].  
52 This idea is well supported by experimental evidence from studies in rhesus monkeys [9,10], rats [11]  
53 and humans [3,12–14]. In addition to motor skill learning, sleep may also be required for motor skill  
54 generalisation [15].

55

56 Schema formation can be broadly defined as the ability to organize a group of facts or experiences  
57 and extract their core gist, thus facilitating integration of new information into pre-existing knowledge  
58 and the repurposing of pre-existing knowledge in novel situations [16]. Just like with motor skills, the  
59 formation and updating of schemas requires time [4,17] and benefits from sleep [4,15,18–21],  
60 particularly REM sleep [18] and sleep spindles [19].

61

62 The fact that both motor skills and schemas require time, potentially even weeks, to develop, could  
63 explain why some studies in humans examining motor sequence learning [22], generalization [23],  
64 extraction of hidden regularities (reviewed in [24]), problem-solving [25] or insight [26] have failed to  
65 find an overnight sleep effect. Such higher order forms of memory reorganization and/or schema  
66 updating may require longer periods of time and multiple sleep opportunities to unfold.

67

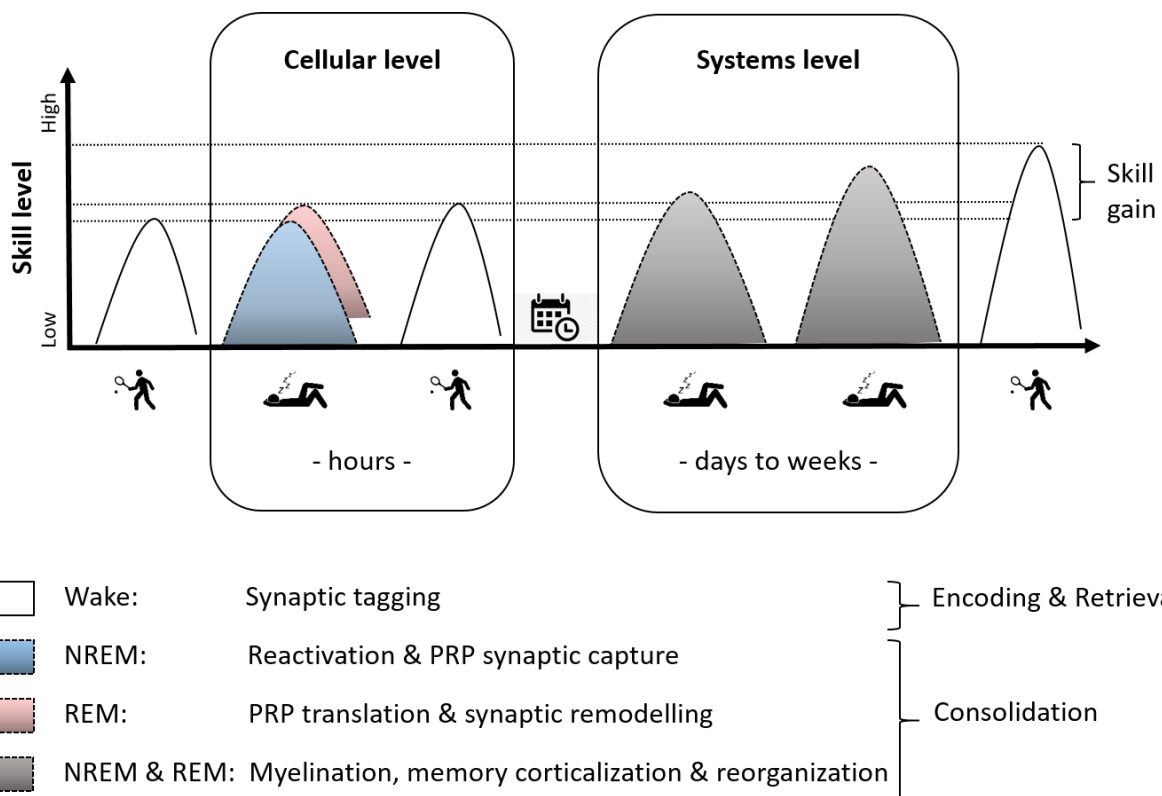
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### 69 **Synaptic and myelin plasticity events during sleep enhance skills and schemas**

70 We propose that the slowly evolving sleep-dependent enhancement of memories, particularly skills  
71 and schemas, is achieved through a series of four steps integrating neuronal and myelin plasticity  
72 leading to molecular, cellular and systems consolidation. According to the new model by Seibt & Frank,  
73 the first step encompasses synaptic tagging and capture of plasticity-related products (PRPs). Synaptic  
74 tagging is mainly accomplished during wakefulness while synaptic capture of PRPs is thought to occur

75 as a consequence of reactivation events during NREM sleep, leading to an immediate stabilization of  
 76 memories [5]. The second step concerns synaptic plasticity and includes PRP translation, spine  
 77 formation and pruning. These events are thought to rely on REM sleep and can occur within a few  
 78 hours of learning [5]. The third and fourth steps, myelin plasticity and memory corticalization &  
 79 reorganization, require a longer period of time to unfold, ranging from days to weeks. These two steps  
 80 could explain the delay observed between learning and performance enhancement. Further details  
 81 on each one of these steps are described below and illustrated in figure 1.

82



**Figure 1. Mechanisms of sleep-dependent slow enhancement of skills and schemas.** During wake, synapses recruited during learning are tagged and plasticity-related products (PRPs) are transcribed. Consolidation at the molecular and cellular levels within the first sleep episode stabilizes the new engram. Reactivation events during NREM sleep trigger PRP capture into tagged synapses. Then, during REM sleep, PRPs are translated and synapses are remodelled. Over the course of the next few days to weeks, myelin plasticity, memory corticalization & reorganization events during sleep continue to unfold, ultimately leading to enhanced performance.

*Step 1: Neuronal priming: memory reactivation, synaptic tagging and capture*

Metaplasticity concerns how neural changes may influence the capacity for future synaptic plasticity (i.e. “plasticity of synaptic plasticity”). Metaplasticity happens at the neuronal level by modulating neuronal excitability, and at the synaptic level, through synaptic tagging and capture (STC). According to the STC hypothesis, synapses are ‘tagged’ at the time of encoding during wakefulness for later remodelling (strengthening or pruning) [27]. The exact nature of the ‘tags’ is still under investigation

98 but it is believed that they can be positive or negative. For example, AMPA receptor internalization  
99 may act as a negative tag, while AMPA receptor insertion or activation may act as a positive tag [5].  
100 Another molecule, Homer1a, has been proposed as a negative tag, which is supported by experimental  
101 evidence implicating it in the homeostatic downscaling of excitatory synapses during sleep [28].  
102 Once synapses have been positively and negatively tagged, they are primed for the capture of PRPs.  
103 PRPs are involved in the stabilization of functional and structural changes to dendritic spines and  
104 include synapse-related immediate early genes such as *bdnf* as well as proteins like PSD95 and the  
105 kinase PKMzeta [5,27].

106  
107 It has been suggested that metaplasticity could be the molecular bridge between plasticity-related  
108 changes occurring in wakefulness and sleep [5]. During wakefulness, experience-dependent  
109 transcription and transport of PRPs to the vicinity of dendrites occurs in a neuron-specific manner,  
110 while positive and negative synaptic tagging accomplishes priming in a synapse-specific manner. The  
111 next step – PRP capture into tagged synapses – must occur within the lifetime of the tag (which ranges  
112 from minutes to hours), so that functional and structural plasticity can be initiated. Seibt and Frank  
113 propose that PRP capture is accomplished during NREM sleep and more specifically, during memory  
114 reactivation [5]. Thus, in this model memory reactivation is an essential pre-requisite for subsequent  
115 plasticity events to take place and if this is the case, it should correlate with memory consolidation.  
116 Zhang and colleagues recently supported this notion using intracranial EEG in presurgical epilepsy  
117 patients by observing a link between spontaneous cortical reactivation and memory consolidation  
118 [29]. Moreover, superior performance on a diverse range of memory tasks has been consistently  
119 observed when reactivation is experimentally triggered using targeted memory reactivation (TMR)  
120 during sleep in humans [30–33].

121  
122 Existing data relate mainly to motor skill tasks [34,35], but could reactivation also reorganize  
123 experiences, thus favouring schema formation through gist extraction and generalization? Liu and  
124 colleagues argue that the answer is yes, as evidenced by the non-invasive detection of human replay  
125 representing the abstract structure of a previously learned sequences of objects [36]. In addition,  
126 replay may even facilitate creative insight, since ‘replay’ of never-experienced potential shortcuts has  
127 been observed after rats explored a new environment [37]. Reactivation has been mostly observed  
128 during NREM sleep [29,38] and wake [39] however, there is evidence that it could also occur during  
129 REM [40–43], and the latter has been shown to predict generalization and schematization of  
130 information [44,45]. Seibt and Frank’s model might therefore benefit from an extension to include a  
131 role for wake and REM reactivation.

132

133 *Step 2: Synaptic plasticity: PRP translation, spine formation and pruning*

134 According to Seibt and Frank, PRPs which were transcribed to mRNA during wake and captured into  
135 synapses during NREM sleep are translated into proteins during REM sleep. This process provides the  
136 protein synthesis required for bidirectional structural plasticity (pruning negatively tagged synapses  
137 and strengthening positively tagged synapses) [5]. In line with this hypothesis, REM sleep has been  
138 observed to play a specific role in pruning, strengthening and maintaining newly formed dendritic  
139 spines in mouse pyramidal neurons following motor learning [46]. This step takes place during the late  
140 phase of skill acquisition, as evidenced by a study in rats using the skilled reaching task showing that  
141 even though reaching accuracy had already improved after 3 days of training, synaptogenesis in the  
142 motor cortex was not detectable until 7 days of training had passed, at which point a further significant  
143 increase in performance was observed [11].

144

145 In the future, it might be interesting to build on Seibt and Frank's model to include evidence  
146 implicating NREM sleep in dendritic spine plasticity [47–49] and homeostatic downscaling [50], as well  
147 as experimental findings linking REM sleep to epigenetic changes [51], gene expression [51] and  
148 microRNA expression [52].

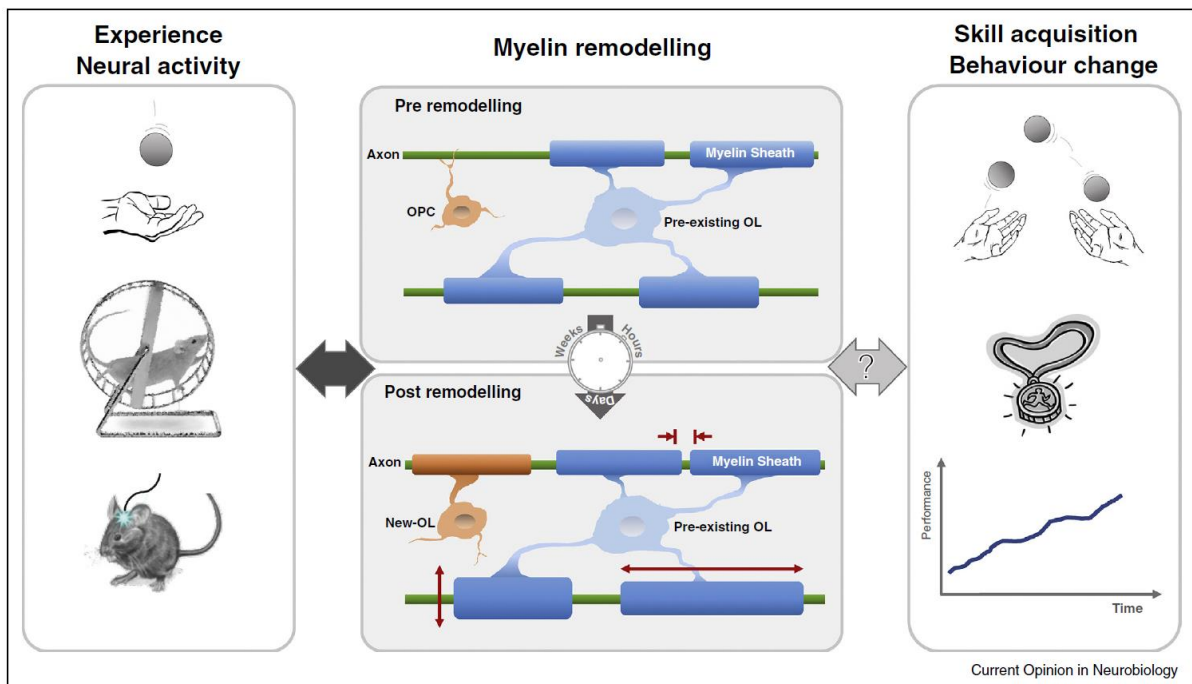
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150 *Step 3: Glial and myelin plasticity*

151 Building on the literature relating to steps 1 and 2 [5,27], we propose that myelination could be the  
152 next step underlying the slow sleep-dependent consolidation and transformation of memories over  
153 time, particularly motor skills and schemas, since: i) both motor and schema learning are slowly  
154 acquired and can benefit from sleep (see Box 1), ii) myelination is triggered after motor [53,54] and  
155 schema learning [55] (see Figure 2), iii) both myelination and improvements in performance occur on  
156 a similar time scale [56] and iv) myelin formation is facilitated during sleep [57].

157

158



159

160 **Figure 2. Myelination and learning.** Experience-dependent activity triggers myelin remodelling over a  
 161 period ranging from hours to weeks, and these changes correlate with behaviour improvements in  
 162 skill acquisition. Figure reproduced from [58].

163

164

165 *Myelination and sleep*

166 Sleep facilitates myelin production [57] and oligodendrocyte activity [59]. Conversely, chronic sleep  
 167 loss in mice results in reduced myelin thickness, an alteration that is not reversed after ~32 h of  
 168 recovery sleep, given the time-consuming nature of myelin plasticity events [60]. Genes involved in  
 169 the synthesis and maintenance of membranes, including myelin, have increased expression during  
 170 sleep in rodents [57]. Myelin is produced by oligodendrocytes, which are also responsible for  
 171 supporting axonal metabolism. Sleep has been suggested to represent the optimal time window for  
 172 the active upkeep of axonal integrity following learning, since oligodendrocytes are less burdened by  
 173 the need to support sustained axonal firing in sleep (reviewed in [59]). Studies in mice suggest that  
 174 REM sleep and its characteristic high cholinergic tone may favour oligodendrocyte precursor cells  
 175 (OPC) proliferation and survival (reviewed in [6]). However, more studies are needed to determine  
 176 whether sleep's overall involvement in myelin plasticity can be attributed to REM sleep specifically or  
 177 to other more general features of this brain state.

178

179 *Step 4: Corticalization and reorganization*

180 In addition to PRP capture [5] and dendritic spine remodelling [46], we believe that REM sleep plays  
 181 an important role in memory corticalization and reorganization [7]. Multiple plasticity waves occur in

182 the days and weeks after a learning episode, probably initiated by NREM reactivations in the  
183 hippocampus and propagated towards the neocortex during REM, leading to memory trace  
184 stabilization [7]. In line with this hypothesis, brain-wide changes in blood volume in rats have been  
185 observed during REM sleep after bursts of theta and gamma hippocampal activity and the trajectory  
186 of these hemodynamic patterns tends to begin in the thalamus, proceed to the hippocampus and then  
187 finally reach the cortex [61].

188

189 The slow process of corticalization may be accompanied by a reorganization of information, evidenced  
190 by formation of associations, gist extraction, generalization and updating of internal models [62]. As  
191 such, a motor skill study in rats showed that, despite significant improvements in performance after 3  
192 days of training, motor map reorganization was not detectable until after 10 days of training [11].

193

194 REM sleep has been implicated in memory reorganization (reviewed in [16]) and REM dreams might  
195 provide an interesting opportunity to sneak a peek into this process [16,63]. According to the Trace-  
196 Spur model, the bizarreness of REM sleep dreams results from synaptic strength modulations allowing  
197 for hyper-associative mental activity, which in turn might set the stage for the restructuring of  
198 experiences [63]. This idea is supported by a dream study in patients suffering from complicated grief,  
199 in which repeated appearance of familiar characters was interpreted as an attempt to reorganize  
200 relational cognitive schemas in order to readjust to the loss [64]. If indeed REM sleep dreams represent  
201 a window from which we can witness the slowly evolving process of memory reorganization, this  
202 might also explain the dream-lag effect, wherein personally significant events are only incorporated  
203 into dreams approximately a week after their occurrence [65].

204

205 It is worth mentioning that, while this model places great emphasis on the role of time in memory  
206 consolidation, our main focus pertains to the function of each sleep stage, rather than the time of day  
207 when they occur and thus the potential influence of circadian rhythm on each one of the 4 steps  
208 outline above remains to be investigated in future studies.

209

#### 210 **Box 2. Brain regions involved in the slow consolidation of skills as proposed in our model**

211 Motor skill memory consolidation is known to rely on a cortico-striato-cerebellar network, as well as  
212 the hippocampus [66]. In line with step 1 of our model, reactivation of ensembles recruited for motor  
213 skill learning has been detected in humans in the striatum [67,68], the motor cortex, the hippocampus  
214 and the cerebellum [68], as well as in the rat motor cortex [69,70] during NREM sleep. Furthermore,  
215 in line with step 2 of our model, REM-related plasticity changes have been found in the rat motor  
216 cortex [71] and REM-related dendritic spine pruning and maintenance has been observed in the  
217 mouse motor cortex [46]. Interestingly, expression of *zif-268*, a gene involved in synaptic plasticity,  
218 has been detected in the amygdala, entorhinal and auditory cortices in the first REM sleep episode,



219 propagating to somatosensory and motor cortices in subsequent REM episodes [71]. Taken together,  
220 these findings highlight not only NREM and REM's contribution to motor memory consolidation in the  
221 relevant brain regions, but also the benefit accrued from successive iterative cycles of each of these  
222 sleep stages [72]. Finally, as proposed in step 3 of our model, after 11 days of training on a new motor  
223 skill, changes in myelination were observed in the rat motor cortex, and these correlated with learning  
224 rate [53].  
225

## 226 **Conclusion**

227 We build on prior models suggesting that NREM and REM sleep play complementary roles in memory  
228 consolidation [5] and reorganization [7], particularly of motor skills and schemas. Specifically, we  
229 argue that NREM may take the lead in the first few minutes to hours after learning by stabilizing  
230 engrams through reactivation and capture of plasticity-related products while REM may then be in  
231 charge of PRP synthesis, spine formation and pruning in the short run (hours-days). Over the course  
232 of next few days to weeks after learning, sleep also supports myelination, memory corticalization and  
233 reorganization. Initial evidence points toward an involvement of REM sleep in these time consuming  
234 processes, however a causal link between the two remains to be established.  
235  
236

237 **References and recommended reading:**

238 Papers of particular interest, published within the period of review, have been highlighted as:

239 • of special interest

240 •• of outstanding interest

- 241 1. Rasch B, Born J: **About Sleep's Role in Memory.** *Physiol Rev* 2013, **93**:681–766.
- 242 2. Klinzing JG, Niethard N, Born J: **Mechanisms of systems memory consolidation during sleep.**  
243 *Nat Neurosci* 2019, doi:10.1038/s41593-019-0467-3.
- 244 3. Walker MP, Brakefield T, Seidman J, Morgan A, Hobson JA, Stickgold R: **Sleep and the Time**  
245 **Course of Motor Skill Learning.** *Learn Mem* 2003, **10**:275–284.
- 246 4. Lutz ND, Diekelmann S, Hinse-Stern P, Born J, Rauss K: **Sleep Supports the Slow Abstraction**  
247 **of Gist from Visual Perceptual Memories.** *Sci Rep* 2017, **7**:42950.
- 248 5. Seibt J, Frank MG: **Primed to Sleep: The Dynamics of Synaptic Plasticity Across Brain States.**  
249 *Front Syst Neurosci* 2019, **13**:2.
- 250 6. Bellesi M: **Sleep and Oligodendrocyte Functions.** *Curr Sleep Med Reports* 2015, **1**:20–26.
- 251 7. Almeida-Filho DG, Queiroz CM, Ribeiro S: **Memory corticalization triggered by REM sleep:**  
252 **mechanisms of cellular and systems consolidation.** *Cell Mol Life Sci* 2018, **75**:3715–3740.
- 253 8. Walker MP: **A refined model of sleep and the time course of memory formation.** *Behav*  
254 *Brain Sci* 2005, **28**:51-64;
- 255 9. Zhou X, Tien RN, Ravikumar S, Chase SM: **Distinct types of neural reorganization during long-**  
256 **term learning.** *J Neurophysiol* 2019, **121**:1329–1341.
- 257 10. Oby ER, Golub MD, Hennig JA, Degenhart AD, Tyler-Kabara EC, Yu BM, Chase SM, Batista AP:  
258 **New neural activity patterns emerge with long-term learning.** *Proc Natl Acad Sci* 2019,  
259 **116**:15210–15215.
- 260 11. Kleim JA, Hogg TM, VandenBerg PM, Cooper NR, Bruneau R, Rempel M: **Cortical**  
261 **Synaptogenesis and Motor Map Reorganization Occur during Late, But Not Early, Phase of**  
262 **Motor Skill Learning.** *J Neurosci* 2004, **24**:628–633.
- 263 12. Morita Y, Ogawa K, Uchida S: **Napping after complex motor learning enhances juggling**  
264 **performance.** *Sleep Sci* 2016, **9**:112–116.
- 265 13. Lugassy D, Herszage J, Pilo R, Brosh T, Censor N: **Consolidation of complex motor skill**  
266 **learning: evidence for a delayed offline process.** *Sleep* 2018, **41**.
- 267 14. Walker MP, Liston C, Hobson JA, Stickgold R: **Cognitive flexibility across the sleep-wake**  
268 **cycle: REM-sleep enhancement of anagram problem solving.** *Brain Res Cogn Brain Res* 2002,  
269 **14**:317–324.
- 270 15. Pettibone WD, Kam K, Chen RK, Varga AW: **Necessity of Sleep for Motor Gist Learning in**

- 271 **Mice.** *Front Neurosci* 2019, **13**:293.
- 272 16. Landmann N, Kuhn M, Maier J-G, Spiegelhalter K, Baglioni C, Frase L, Riemann D, Sterr A,  
273 Nissen C: **REM sleep and memory reorganization: Potential relevance for psychiatry and**  
274 **psychotherapy.** *Neurobiol Learn Mem* 2015, **122**:28–40.
- 275 17. Gilboa A, Marlatte H: **Neurobiology of Schemas and Schema-Mediated Memory.** *Trends*  
276 *Cogn Sci* 2017, **21**:618–631.
- 277 18. Durrant SJ, Cairney SA, McDermott C, Lewis PA: **Schema-conformant memories are**  
278 **preferentially consolidated during REM sleep.** *Neurobiol Learn Mem* 2015, **122**:41–50.
- 279 19. Hennies N, Lambon Ralph MA, Kempkes M, Cousins JN, Lewis PA: **Sleep Spindle Density**  
280 **Predicts the Effect of Prior Knowledge on Memory Consolidation.** *J Neurosci* 2016, **36**:3799–  
281 3810.
- 282 20. Humiston GB, Wamsley EJ: **Unlearning implicit social biases during sleep: A failure to**  
283 **replicate.** *PLoS One* 2019, **14**:e0211416.
- 284 21. Hu X, Antony JW, Creery JD, Vargas IM, Bodenhausen G V, Paller KA: **Unlearning implicit**  
285 **social biases during sleep.** *Science (80- )* 2015, **348**:1013–1015.
- 286 22. Rickard TC, Cai DJ, Rieth CA, Jones J, Ard MC: **Sleep does not enhance motor sequence**  
287 **learning.** *J Exp Psychol Learn Mem Cogn* 2008, **34**:834–42.
- 288 23. Sweegers CCG, Talamini LM: **Generalization from episodic memories across time: A route for**  
289 **semantic knowledge acquisition.** *Cortex* 2014, **59**:49–61.
- 290 24. Lerner I, Gluck MA: **Sleep and the extraction of hidden regularities: A systematic review and**  
291 **the importance of temporal rules.** *Sleep Med Rev* 2019, **47**:39–50.
- 292 25. Brodt S, Pöhlchen D, Täumer E, Gais S, Schönauer M: **Incubation, not sleep, aids problem**  
293 **solving.** *Sleep* 2018, doi:10.1093/sleep/zsy155.
- 294 26. Schönauer M, Brodt S, Pöhlchen D, Breßmer A, Danek AH, Gais S: **Sleep Does Not Promote**  
295 **Solving Classical Insight Problems and Magic Tricks.** *Front Hum Neurosci* 2018, **12**:72.
- 296 27. Redondo RL, Morris RGM: **Making memories last: the synaptic tagging and capture**  
297 **hypothesis.** *Nat Neurosci Rev* 2011, **12**:17–30.
- 298 28. Diering GH, Nirujogi RS, Roth RH, Worley PF, Pandey A, Huganir RL: **Homer1a drives**  
299 **homeostatic scaling-down of excitatory synapses during sleep.** *Science (80- )* 2017, **355**:511–  
300 515.
- 301 29. Zhang H, Fell J, Axmacher N: **Electrophysiological mechanisms of human memory**  
302 **consolidation.** *Nat Commun* 2018, **9**:4103.
- 303 30. Cairney SA, Guttesen A á V, El Marj N, Staresina BP: **Memory Consolidation Is Linked to**  
304 **Spindle-Mediated Information Processing during Sleep.** *Curr Biol* 2018,

- 305 doi:10.1016/j.cub.2018.01.087.
- 306 31. Schreiner T, Doeller CF, Jensen O, Rasch B, Staudigl T: **Theta Phase-Coordinated Memory**  
307 **Reactivation Reoccurs in a Slow-Oscillatory Rhythm during NREM Sleep.** *Cell Rep* 2018,  
308 **25:296–301.**
- 309 32. Belal S, Cousins J, El-Deredy W, Parkes L, Schneider J, Tsujimura H, Zoumpoulaki A, Perapoch  
310 M, Santamaria L, Lewis P: **Identification of memory reactivation during sleep by EEG**  
311 **classification.** *Neuroimage* 2018, **176:203–214.**
- 312 33. Shanahan LK, Gjorgieva E, Paller KA, Kahnt T, Gottfried JA: **Odor-evoked category**  
313 **reactivation in human ventromedial prefrontal cortex during sleep promotes memory**  
314 **consolidation.** *Elife* 2018, **7.**
- 315 34. Antony JW, Gobel EW, O'Hare JK, Reber PJ, Paller K a: **Cued memory reactivation during**  
316 **sleep influences skill learning.** *Nat Neurosci* 2012, **15:1114–1116.**
- 317 35. Schönauer M, Geisler T, Gais S: **Strengthening procedural memories by reactivation in sleep.**  
318 *J Cogn Neurosci* 2014, **26:143–53.**
- 319 36. Liu Y, Dolan RJ, Kurth-Nelson Z, Behrens TEJ: **Human Replay Spontaneously Reorganizes**  
320 **Experience.** *Cell* 2019, **178:640-652.e14.**
- 321 37. Gupta AS, van der Meer MAA, Touretzky DS, Redish AD: **Hippocampal Replay Is Not a Simple**  
322 **Function of Experience.** *Neuron* 2010, **65:695–705.**
- 323 38. Bergmann TO, Mölle M, Diedrichs J, Born J, Siebner HR: **Sleep spindle-related reactivation of**  
324 **category-specific cortical regions after learning face-scene associations.** *Neuroimage* 2012,  
325 **59:2733–2742.**
- 326 39. Atherton LA, Dupret D, Mellor JR: **Memory trace replay: the shaping of memory**  
327 **consolidation by neuromodulation.** *Trends Neurosci* 2015, doi:10.1016/j.tins.2015.07.004.
- 328 40. Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips C, Aerts J, Del Fiore G, Degueldre  
329 C, Meulemans T, et al.: **Experience-dependent changes in cerebral activation during human**  
330 **REM sleep.** *Nat Neurosci* 2000, **3:831–6.**
- 331 41. Peigneux P, Laureys S, Fuchs S, Destrebecqz A, Collette F, Delbeuck X, Phillips C, Aerts J, Del  
332 Fiore G, Degueldre C, et al.: **Learned material content and acquisition level modulate**  
333 **cerebral reactivation during posttraining rapid-eye-movements sleep.** *Neuroimage* 2003,  
334 **20:125–34.**
- 335 42. Louie K, Wilson MA: **Temporally structured replay of awake hippocampal ensemble activity**  
336 **during rapid eye movement sleep.** *Neuron* 2001, **29:145–56.**
- 337 43. Dumoulin Bridi MC, Aton SJ, Seibt J, Renouard L, Coleman T, Frank MG: **Rapid eye movement**  
338 **sleep promotes cortical plasticity in the developing brain.** *Sci Adv* 2015, **1:e1500105.**

- 339 44. Sterpenich V, Schmidt C, Albouy G, Matarazzo L, Vanhaudenhuyse A, Boveroux P, Degueldre  
340 C, Leclercq Y, Balteau E, Collette F, et al.: **Memory reactivation during rapid eye movement**  
341 **sleep promotes its generalization and integration in cortical stores.** *Sleep* 2014, **37**:1061–75,  
342 1075A-1075B.
- 343 45. Tamminen J, Lambon Ralph MA, Lewis PA: **Targeted memory reactivation of newly learned**  
344 **words during sleep triggers REM-mediated integration of new memories and existing**  
345 **knowledge.** *Neurobiol Learn Mem* 2017, **137**:77–82.
- 346 46. Li W, Ma L, Yang G, Gan W-B: **REM sleep selectively prunes and maintains new synapses in**  
347 **development and learning.** *Nat Neurosci* 2017, **20**:427–437.
- 348 47. Seibt J, Richard CJ, Sigl-Glöckner J, Takahashi N, Kaplan DI, Doron G, de Limoges D, Bocklisch  
349 C, Larkum ME: **Cortical dendritic activity correlates with spindle-rich oscillations during**  
350 **sleep in rodents.** *Nat Commun* 2017, **8**:684.
- 351 48. Niethard N, Ngo H-V V., Ehrlich I, Born J: **Cortical circuit activity underlying sleep slow**  
352 **oscillations and spindles.** *Proc Natl Acad Sci* 2018, **115**:E9220–E9229.
- 353 49. Yang G, Lai CSW, Cichon J, Ma L, Li W, Gan W-B: **Sleep promotes branch-specific formation of**  
354 **dendritic spines after learning.** *Science* 2014, **344**:1173–8.
- 355 50. Tononi G, Cirelli C: **Sleep and the price of plasticity: from synaptic and cellular homeostasis**  
356 **to memory consolidation and integration.** *Neuron* 2014, **81**:12–34.
- 357 51. Narwade SC, Mallick BN, Deobagkar DD: **Transcriptome Analysis Reveals Altered Expression**  
358 **of Memory and Neurotransmission Associated Genes in the REM Sleep Deprived Rat Brain.**  
359 *Front Mol Neurosci* 2017, **10**:67.
- 360 52. Karabulut S, Korkmaz Bayramov K, Bayramov R, Ozdemir F, Topaloglu T, Ergen E, Yazgan K,  
361 Taskiran AS, Golgeli A: **Effects of post-learning REM sleep deprivation on hippocampal**  
362 **plasticity-related genes and microRNA in mice.** *Behav Brain Res* 2019, **361**:7–13.
- 363 53. Sampaio-Baptista C, Khrapitchev AA, Foxley S, Schlagheck T, Scholz J, Jbabdi S, DeLuca GC,  
364 Miller KL, Taylor A, Thomas N, et al.: **Motor Skill Learning Induces Changes in White Matter**  
365 **Microstructure and Myelination.** *J Neurosci* 2013, **33**:19499–19503.
- 366 54. Lakhani B, Borich MR, Jackson JN, Wadden KP, Peters S, Villamayor A, MacKay AL, Vavasour  
367 IM, Rauscher A, Boyd LA: **Motor Skill Acquisition Promotes Human Brain Myelin Plasticity.**  
368 *Neural Plast* 2016, **2016**:1–7.
- 369 55. Hasan M, Kanna MS, Jun W, Ramkrishnan AS, Iqbal Z, Lee Y, Li Y: **Schema-like learning and**  
370 **memory consolidation acting through myelination.** *FASEB J* 2019,  
371 doi:10.1096/fj.201900910R.
- 372 56. McKenzie IA, Ohayon D, Li H, Paes de Faria J, Emery B, Tohyama K, Richardson WD: **Motor**

- 373 **skill learning requires active central myelination.** *Science (80- )* 2014, **346**:318–322.
- 374 57. Bellesi M, Pfister-Genskow M, Maret S, Keles S, Tononi G, Cirelli C: **Effects of Sleep and Wake**  
375 **on Oligodendrocytes and Their Precursors.** *J Neurosci* 2013, **33**:14288–14300.
- 376 58. Kaller MS, Lazari A, Blanco-Duque C, Sampaio-Baptista C, Johansen-Berg H: **Myelin plasticity**  
377 **and behaviour — connecting the dots.** *Curr Opin Neurobiol* 2017, **47**:86–92.
- 378 59. de Vivo L, Bellesi M: **The role of sleep and wakefulness in myelin plasticity.** *Glia* 2019,  
379 doi:10.1002/glia.23667.
- 380 60. Bellesi M, Haswell JD, de Vivo L, Marshall W, Roseboom PH, Tononi G, Cirelli C: **Myelin**  
381 **modifications after chronic sleep loss in adolescent mice.** *Sleep* 2018, **41**.
- 382 61. Bergel A, Deffieux T, Demené C, Tanter M, Cohen I: **Local hippocampal fast gamma rhythms**  
383 **precede brain-wide hyperemic patterns during spontaneous rodent REM sleep.** *Nat*  
384 *Commun* 2018, **9**:5364.
- 385 62. Landmann N, Kuhn M, Piosczyk H, Feige B, Baglioni C, Spiegelhalter K, Frase L, Riemann D,  
386 Sterr A, Nissen C: **The reorganisation of memory during sleep.** *Sleep Med Rev* 2014,  
387 doi:10.1016/j.smrv.2014.03.005.
- 388 63. Voss U, Klimke A: **Dreaming during REM sleep: autobiographically meaningful or a simple**  
389 **reflection of a Hebbian-based memory consolidation process?** *Arch Ital Biol* 2018, **156**:99–  
390 111.
- 391 64. Germain A, Shear KM, Walsh C, Buysse DJ, Monk TH, Reynolds CF, Frank E, Silowash R: **Dream**  
392 **Content in Complicated Grief: A Window into Loss-Related Cognitive Schemas.** *Death Stud*  
393 2013, **37**:269–284.
- 394 65. Eichenlaub J-B, Cash SS, Blagrove M: **Daily Life Experiences in Dreams and Sleep-Dependent**  
395 **Memory Consolidation.** Springer International Publishing; 2017:161–172.
- 396 66. Albouy G, King BR, Maquet P, Doyon J: **Hippocampus and striatum: dynamics and interaction**  
397 **during acquisition and sleep-related motor sequence memory consolidation.** *Hippocampus*  
398 2013, **23**:985–1004.
- 399 67. Fogel S, Albouy G, King BR, Lungu O, Vien C, Bore A, Pinsard B, Benali H, Carrier J, Doyon J:  
400 **Reactivation or transformation? Motor memory consolidation associated with cerebral**  
401 **activation time-locked to sleep spindles.** *PLoS One* 2017, **12**:e0174755.
- 402 68. Cousins JN, El-Deredy W, Parkes LM, Hennies N, Lewis PA: **Cued Reactivation of Motor**  
403 **Learning during Sleep Leads to Overnight Changes in Functional Brain Activity and**  
404 **Connectivity.** *PLoS Biol* 2016, **14**:e1002451.
- 405 69. Ramanathan DS, Gulati T, Ganguly K: **Sleep-Dependent Reactivation of Ensembles in Motor**  
406 **Cortex Promotes Skill Consolidation.** *PLoS Biol* 2015, **13**:e1002263.

- 407 70. Gulati T, Ramanathan DS, Wong CC, Ganguly K: **Reactivation of emergent task-related**  
408 **ensembles during slow-wave sleep after neuroprosthetic learning.** *Nat Neurosci* 2014,  
409 **17:1107–13.**
- 410 71. Ribeiro S, Mello C V., Velho T, Gardner TJ, Jarvis ED, Pavlides C: **Induction of hippocampal**  
411 **long-term potentiation during waking leads to increased extrahippocampal zif-268**  
412 **expression during ensuing rapid-eye-movement sleep.** *J Neurosci* 2002, **22:10914–10923.**
- 413 72. Lewis PA, Knoblich G, Poe G: **How Memory Replay in Sleep Boosts Creative Problem-Solving.**  
414 *Trends Cogn Sci* 2018, **22:491–503.**

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#### 416 **Reference Annotations**

417 [5] •• A review proposing a model to explain how different plasticity events underlying molecular and  
418 cellular consolidation may be distributed across brain states and how they related to each other.

419 [7] •• A review proposing a role of REM sleep in the corticalization of memories within the framework  
420 of contextual fear learning in rats

421 [36] •• A MEG study in humans showing that memory replay during wake can facilitate the  
422 reorganization of experiences.

423 [46] •• An animal study in mice showing that REM sleep is involved in pruning and strengthening of  
424 newly formed synapses after motor learning, using a selective sleep deprivation paradigm.

425 [55] •• The first study showing that schema learning is accompanied by an increase in newly formed  
426 oligodendrocyte progenitor cells an in myelin strength in the anterior cingulate cortex.

427 [60] • An animal study showing that 5 days of chronic sleep restriction in mice leads to a reduction in  
428 myelin thickness.

429 [61] • An animal study in rats using functional ultrasound imaging concurrently with recordings of  
430 local-field potentials to show that hippocampal fast gamma activity precedes hemodynamic patterns,  
431 which tended to begin in the thalamus and proceed to the hippocampus and finally the cortex.

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