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# The role of sleep in emotional processing: insights and unknowns from rodent research

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## Abstract

Sleep is essential for the regulation of neural dynamics and animal behavior. In particular, sleep is crucial for memory consolidation and emotional regulation. In turn, emotions are key to the modulation of learning processes in which sleep also plays a crucial role. Emotional processing triggers coordinated activity between neuronal populations embedded in a network including the hippocampus, amygdala and prefrontal cortex. The optogenetic modulation of these distributed engrams' activity interferes with emotional memory. During non-REM sleep, cross-structure coordinated replay may underpin the consolidation of brain-wide emotional associative engrams. Fear conditioning induces neural synchronization between the amygdala, hippocampus, and medial prefrontal cortex during subsequent REM sleep, the perturbation of which interferes with fear memory consolidation. Future work may focus on the differential mechanisms during REM vs non-REM sleep that underpin emotional regulation and memory consolidation, as well as on distinguishing between these two tightly linked cognitive processes.

## Introduction

Sleep is a ubiquitous phenomenon throughout the animal kingdom and is vital for the brain to function properly. Indeed, a lack of sleep leads to a constellation of cognitive and behavioral alterations (Krause et al. 2017), and at least two cognitive processes have been critically linked to sleep. The first one is memory consolidation (Klinzing et al. 2019), i.e. the gradual strengthening

31 of memories over time. The second is emotional regulation, allowing for the maintenance of an  
32 appropriate level of reactivity to emotional situations (let he who has never experienced irritability  
33 or even outbursts of rage/tears when sleep-deprived cast the first pillow). The intensity and  
34 vividness of emotions during dreams has also been a constant subject of great fascination in art  
35 (Fig. 1) and conversation in everyday life, driving early studies on the link between dreams, sleep,  
36 and emotions in neuroscience.  
37



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39 *John Henry Fuseli - The nightmare, Oil on canvas, 1781.*

40 Emotions can strengthen memories: we remember events that carried strong positive or  
41 negative emotional weight better and more vividly. Sometimes we even re-experience these  
42 emotions when exposed to reminders of the event, such as the context. For instance, you will feel  
43 fear when walking down a street where you were bitten by a dog, a phenomenon similar to  
44 Pavlovian conditioning. These associative memories, although critical to avoid danger and

45 promoting survival, can become maladaptive in patients suffering from trauma and stressor-related  
46 disorders such as post-traumatic stress disorder (PTSD), a mental condition associated with sleep  
47 disturbances and severe nightmares (Colvonen et al. 2019). In short, sleep seems to be pivotal in  
48 “emotional processing”, an umbrella term used to encapsulate i) emotional associative memory  
49 consolidation, ii) the modulation of episodic memory by emotions and iii) emotional  
50 regulation (Tempesta et al. 2016).

51 Sleep itself is composed of several different stages associated with distinct physiological features  
52 occurring in cycles throughout the night. Although it is an oversimplification, a main distinction can  
53 be made between rapid eye movement (REM) sleep and non-REM sleep. REM sleep is also called  
54 paradoxical sleep because the EEG (or LFP for intracranial recordings) is very similar to  
55 wakefulness, but associated with complete muscle atonia. Non-REM sleep encompasses several  
56 substages during which the non-REM characteristic rhythms (spindles, K-complexes, slow  
57 oscillations, hippocampal ripples) occur in varying proportions. In humans, the role of sleep in  
58 emotional processing has been extensively investigated using a wide variety of  
59 approaches. Typically, studies measure emotional reactivity and/or learning and correlate their  
60 related neural activity (fMRI, EEG) with sleep features such as the relative quantity of REM and  
61 non-REM sleep, the structure, quality, and quantity of sleep, EEG features (sleep oscillations) or  
62 sleep manipulations (sleep deprivation). For example, hearing one’s own recorded voice butchering  
63 a karaoke song triggers feelings of shame and embarrassment associated with an fMRI activation  
64 of the amygdala, a core structure for the processing of emotions. Normal REM sleep, but not  
65 fractioned REM sleep, leads to a decrease in amygdala reactivity upon hearing the recording the  
66 following day (Wassing et al. 2019). The effect also correlates with the spindle-rich period  
67 preceding REM sleep recorded by EEG, hinting at the importance of transition periods, and  
68 potentially the alternation between sleep stages. There are a number of excellent reviews exposing  
69 the current landscape of research about the role of sleep in emotional processing in  
70 humans (Krause et al. 2017; Tempesta et al. 2018; Klinzing et al. 2019; Murkar and DeKoninck  
71 2018).

72 While it appears from the human literature that sleep is indeed crucial to emotional processing, no  
73 clear consensus has yet emerged about the respective roles of REM or non-REM sleep. It is also  
74 still unclear whether emotional associative memory, the influence of emotions on memory, and  
75 emotional regulation are distinct or overlapping processes associated with specific sleep stages or  
76 rhythms. To gain further insights into the neural bases that sustain the role of sleep in emotional

77 processing, one has to turn to model organisms where the range of available technologies and  
78 experimental designs allows the observation and manipulation of neural networks with a better  
79 spatial and temporal resolution. In particular, the advent of optogenetic tools for real-time close-  
80 loop manipulation has enabled the activation or inhibition of neural responses during specific sleep  
81 events (short REM sleep episodes or specific oscillations) detected “on-the-fly” (Jego et al. 2013;  
82 Boyce et al. 2016; Van de Ven et al. 2016). Here we will provide an overview of the recent  
83 developments in rodent research about the role of sleep in emotional processing at the systems  
84 level (cellular and molecular mechanisms for emotional plasticity are beyond the scope of this  
85 review), with a particular focus on aversive and appetitive associative learning.

## 86 **Associative learning and the engram as a model for emotional memories in rodents**

87 Memories are thought to be stored and retrieved within specific neuronal ensembles called  
88 “engrams” (Davis and Reijmers 2018; Josselyn and Tonegawa 2020), which are initially recruited  
89 during acquisition. Distributed engram ensembles for emotional memory encompass several brain  
90 regions including the hippocampus, the prefrontal cortex and the amygdala. In particular, the  
91 basolateral amygdala (BLA) is where the emotional valence of a stimulus (aversive or  
92 appetitive; Zhang et al. 2020; Janak and Tye 2015) is associated with a sensory and/or contextual  
93 stimulus in conditioning paradigms (Vetere et al. 2019). The optogenetic activation of engram cells  
94 in the hippocampus, cortex or BLA triggers emotional memory retrieval, while their silencing blocks  
95 it (Trousseau et al. 2016; Ohkawa et al. 2015; Josselyn and Tonegawa 2020; Vetere et al.  
96 2019). Most engram studies explore how events are initially encoded into engrams, and how  
97 memory retrieval relies on the same or modified engram at various timepoints after encoding. This  
98 suggests the existence of “off-line” consolidation and maturation processes that change the  
99 structure of the brain-wide engram over time between encoding and retrieval. For example,  
100 Kitamura et al. (2017) used complex engram tagging, inhibition and reactivation at remote and  
101 recent timepoints after learning in mice to show that immature engram ensembles are formed at  
102 the time of the contextual fear acquisition (Fig. 2) in the HPC, BLA and mPFC. The PFC part of  
103 the engram becomes functional and is required only during remote recall. Indeed, a reorganization  
104 of the emotional memory network gradually takes place throughout the 12 to 30 day period  
105 following acquisition (Vetere et al. 2017).

106 During this consolidation phase between acquisition and retrieval, animals cycle through different  
107 behavioral states, including NREM and REM sleep. For example, REM sleep deprivation after

contextual fear conditioning (Fig. 2) impairs remote, but not recent, emotional memory and alters the network activated during remote retrieval (Rosier et al. 2018), suggesting that early sleep phases after fear acquisition could “set up” the system for systems consolidation. Total sleep deprivation impairs the retrieval of a contextual fear memory, and decreases c-fos expression in the BLA upon retrieval, suggesting that sleep might be instrumental for the proper recruitment of the BLA part of the engram at retrieval (Montes-Rodríguez et al. 2019). Still, there are overall surprisingly few studies addressing the nature of enduring changes in memory engram cells during this “offline” state and post-learning sleep period. Recent studies provide evidence of a link between engram consolidation and post-learning engram cell reactivation in the hippocampus (Choi et al. 2018; Ghandour et al. 2019; Chen et al. 2018). Choi et al (2018) revealed increased structural and functional connectivity between contextual fear engram cells in the mouse hippocampus, associated with increased memory strength. A more recent work determined that hippocampal engram cells formed during learning and reactivated during sleep sessions (NREM or REM) are mostly reinstated during retrieval, in a context-specific manner (Ghandour et al. 2019). Such reactivation during the post-learning sleep period could represent a time-window for the strengthening of existing synapses between engram cells.

#### **Processing emotions during sleep: non-REM sleep and hippocampal ripples**

Memory consolidation during sleep has been extensively studied in rodents through the lens of replay of place cells in the hippocampus. Indeed, during Non-REM sleep ripples, entire sequences of place cells are reactivated: the neural activity of the previous wakefulness epoch is reinstated during the subsequent sleep epoch (“replay”; see Foster [2017] for a review). Suppressing hippocampal ripples - and therefore the associated neuronal activity (putative replay) – in rats during non-REM sleep following training on a spatial task impairs subsequent performance (Girardeau et al. 2009; Ego-Stengel and Wilson 2010), establishing the crucial role of ripples and replay in spatial memory consolidation. Hippocampal reactivations during sleep are increased (O’Neill et al. 2008; McNamara et al. 2014) and prolonged (Giri et al. 2019) after the exploration of novel environments compared to familiar ones. It is difficult to evaluate the emotional valence associated with novelty in rodents, which may be a mix of fear and excitement triggering increased arousal. These results nevertheless suggest that the change in emotional tone might sustain the increased replay following the exploration of a novel environment. Further backing this hypothesis, reward or direct activation of hippocampal dopaminergic fibers during spatial



139 learning promote subsequent ripple-associated hippocampal reactivations (McNamara et al. 2014;  
140 Singer and Frank 2009).

141 The hippocampal representation of space itself is also modulated by emotions during the memory  
142 encoding phase. Indeed, emotional contingencies directly influence place-cell firing (Hok et al.  
143 2007; Hollup et al. 2001; Donzis et al. 2013; Moita et al. 2003). A specific non-place, reward-coding  
144 population was even recently described in the hippocampus (Gauthier and Tank 2018). Therefore,  
145 the effects of emotions on memory are likely initiated during training and prolonged during  
146 consolidation. Interestingly, pharmacological or optogenetic activation or inhibition of the BLA  
147 following training in rats bidirectionally modulate spatial aversive memory consolidation  
148 (Vazdarjanova et al. 1999; Huff et al. 2013). However, it is still unknown how aversive (as opposed  
149 to reward-related) stimuli influence subsequent replay during sleep.

150 Interestingly, pairing the activation during non-REM sleep of one specific place cell with a  
151 pleasurable stimulation of the medial forebrain bundle (MFB) in mice induces an artificial place  
152 preference after sleep for the location associated with the place cell (de Lavilléon et al. 2015). This  
153 suggests that the emotional valence of spatial representation can be updated throughout memory  
154 consolidation during sleep. Similarly, during wakefulness the emotional valence of a given stimulus  
155 is constantly updated by experience. In Pavlovian conditioning protocols, the repetitive exposure  
156 to a stimulus or a context (the conditioned stimulus, CS) previously paired with an aversive or  
157 appetitive unconditioned stimulus (US) induces extinction of the behavior associated with the US.  
158 Importantly, during sleep, the presentation of the CS alone has a different effect. Indeed,  
159 reinstating an olfactory CS during non-REM sleep improves an odor-shock associative memory  
160 (Barnes and Wilson 2014; Rolls et al. 2013; but see Purple et al. 2017), whereas the same  
161 reinstatement during wakefulness triggers extinction (Barnes and Wilson 2014).

162 In short, activating part of a memory trace during sleep might be recruiting the complementary part  
163 of the engram through cross-structure pattern completion that would reinforce the associative  
164 memory. Indeed, cross-structure reactivations have been described between the rat hippocampus  
165 and basolateral amygdala (BLA) during non-REM sleep following an aversive spatial learning  
166 task (Girardeau et al. 2017). These joint reactivations occurred preferentially during hippocampal  
167 ripples, and were biased towards the aversive locations. Although the temporality of the  
168 hippocampus-BLA reactivations remains to be assessed, reactivations of the spatial context during  
169 ripples in the hippocampus might trigger the recruitment of the amygdala part of the engram,

170 thereby reinforcing the connections between the two. In fact, this can be done artificially during  
171 wakefulness by activating separately tagged hippocampal “spatial” and BLA “shock” engrams  
172 together to create a *de novo* aversive associative memory (Ohkawa et al. 2015). On a side note,  
173 the activity of amygdalar neurons in monkeys learning an appetitive or aversive tone-odor pairing  
174 reverberates during the post-trial epochs (Reitich-Stolero et al., 2019), suggesting the existence  
175 of “replay-like” mechanisms in the BLA during quiet wakefulness at least.

176 Coordinated activation between neurons of the hippocampus and ventral striatum has also been  
177 reported during the acquisition of place-reward tasks (Sosa et al. 2019), and the following NREM  
178 (but not REM) sleep epoch. These reactivations occur during ripples and the hippocampus tends  
179 to lead the reactivations (Lansink et al. 2008; Lansink et al. 2009; Pennartz et al. 2004).  
180 Dopaminergic VTA neurons that have reward or aversive stimulus-related activity also reactivate  
181 during sleep (Valdés et al. 2015); however, VTA replay in coordination with hippocampal place-  
182 cells and ripples is restricted to quiet wakefulness and does not occur during NREM sleep *per*  
183 *se* (Gomperts et al. 2015).

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185

## 186 **Processing emotions during sleep: REM sleep and theta oscillations**

187 The main electrophysiological characteristic of REM sleep identified so far is the presence of strong  
188 hippocampal theta oscillations. Oscillations in general are believed to coordinate neuronal firing  
189 between distant structures, including the hippocampus-amygdala-prefrontal cortex network crucial  
190 to emotional memory (Popa et al. 2010; Courtin et al. 2014; Likhtik et al. 2014; Stujenske et al.  
191 2014; Karalis et al. 2016; Dejean et al. 2016; Davis et al. 2017; Ahlgrim and Manns 2019). In a  
192 seminal paper, Popa et al. (2010) showed that the coherence at theta frequency between the BLA  
193 and the hippocampus, as well as between the BLA and the medial prefrontal cortex was increased  
194 during REM sleep following training on auditory fear conditioning compared to the preceding REM  
195 sleep. Moreover, the performance at retrieval 24h later correlated with these changes in  
196 coherence. More recently, Boyce et al. (2016) used optogenetics to silence GABAergic neurons  
197 of the medial septum, the major theta-generator, specifically during REM sleep following several  
198 behavioral tasks in mice. Effectively shutting down theta oscillations during REM sleep, they  
199 showed that performance is impaired on the novel object recognition task (hippocampus-  
200 dependent), and in contextual fear conditioning (Fig. 2; both hippocampus and BLA-dependent).



201 Interestingly, there is no impairment in conditioning to the auditory cue, which relies on the BLA  
202 but is hippocampus-independent. Similarly, post-training pharmacological blockade of gap-  
203 junctions, which impairs theta oscillations, prevents the consolidation of contextual, but not cued,  
204 fear conditioning (Bissiere et al. 2011), although the manipulation here wasn't restricted to REM  
205 sleep. Theta oscillations during REM sleep are therefore a good candidate for offline coordinated  
206 activity related to emotional processing (Genzel et al. 2015; Totty et al. 2017). REM sleep is  
207 modified after both appetitive and aversive training (Genzel et al. 2015; Datta 2000), while total  
208 and selective REM sleep deprivations after training impairs emotional memory consolidation and  
209 prevents the related network reorganization (Rosier et al. 2018; Graves et al. 2003; Ravassard et  
210 al. 2016; Ognjanovski et al. 2018).

211 The control of REM sleep (transitions from NREM to REM, REM to wake, duration and quantity of  
212 REM sleep episodes) involves a number of structures and neurons, the exquisite complexity of  
213 which is being gradually revealed (reviewed in Peever and Fuller 2017). REM sleep control is  
214 traditionally studied separately from REM sleep functions, including the emotional processing  
215 function. Nevertheless, activating REM-promoting melanin concentrating hormone-producing  
216 (MCH) neurons in the hypothalamus impairs contextual (but once again, not cued) fear  
217 conditioning, while inhibiting them promotes contextual fear memory consolidation (Izawa et al.  
218 2019). However, it is yet unknown how MCH neurons manipulations affect REM sleep theta  
219 oscillations and hippocampal neural activity during REM. This paper is also conceptually  
220 interesting because it suggests that the circuits controlling REM sleep and those underlying its  
221 mnemonic and emotional functions could be widely overlapping. In that same line of thought,  
222 pontine waves (P-waves) originating from the brainstem (which is instrumental for sleep-wake  
223 regulation), occur primarily during REM sleep and were shown to coordinate with theta  
224 oscillations (Tsunematsu et al. 2020). P-waves density also correlates with the successful  
225 extinction of contextual fear-conditioning (Datta and O'Malley 2013). Overall, this literature  
226 suggests that theta oscillations during REM sleep might be involved in the consolidation of the  
227 contextual information, rather than the *association* between the shock and contextual information.  
228 This corpus of findings is at odds with the fact that neither hippocampal nor hippocampus-  
229 amygdala replay has been reliably shown during REM sleep (Louie and Wilson 2001; Girardeau  
230 et al. 2017), and that typically REM sleep has been viewed as a stage beneficial to emotional  
231 processing (Genzel et al. 2015) rather than spatial memory. Further work is needed to resolve this  
232 paradox.

## 233 Open questions, challenges and future directions

234 The title “the role of sleep in emotional processing” hides a nebulous, multidimensional field of  
235 research where isolated bursts of knowledge, some reviewed here, are still in need of a unifying  
236 theory, if there can be one. Indeed, sleep itself is divided into several distinct stages, defined  
237 differently across species (Blumberg et al. 2020) and under the control of an immensely complex  
238 network of structures involving a delicate balance of neurotransmitters and hormones that is not  
239 yet fully understood (Donlea et al. 2017). In addition, “emotional processing” covers several  
240 concepts including emotional regulation, associative memory (aversive and appetitive  
241 conditioning), episodic memories associated with an emotional weight and the modulation of  
242 memories by emotions.

243 From the current state of knowledge, one emerging hypothesis is that non-REM sleep is involved  
244 in consolidating contextual associative memories via ripple-related coordination with other  
245 structures involved in appetitive and aversive memories. REM sleep, on the other hand, could have  
246 different roles depending on the brain structure and type of memory. Because most studies show  
247 an effect on contextual, but not cued, fear conditioning, REM could selectively influence the  
248 hippocampal part of the emotional engram via theta oscillations, while having a yet undefined  
249 regulatory role on amygdala function and potentially other non-neocortical structures. It is also  
250 possible that the “alternation” between non-REM and REM sleep is required for either emotional  
251 regulation and/or emotional memory consolidation (Puentes-Mestril et al. 2019).

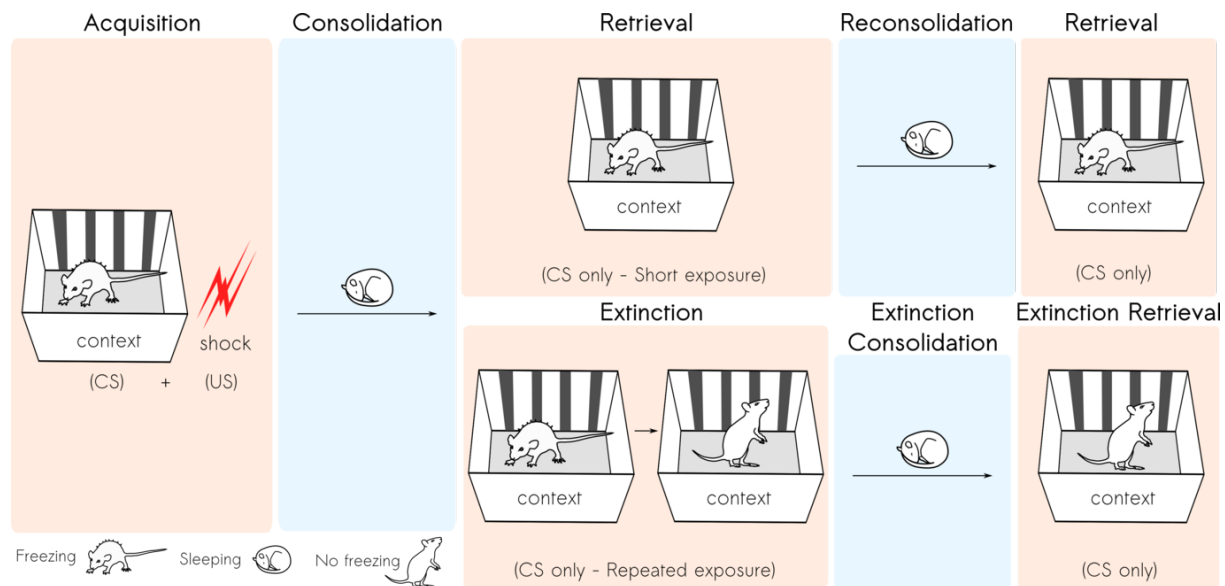
252 A few studies in recent years started to investigate the mechanisms underlying sleep consolidation  
253 of the Pavlovian conditioning memory. However, whether similar or different mechanisms also  
254 underlie extinction memory consolidation remains unanswered. Another general pending question  
255 about emotional memory processes is whether the neural mechanisms and circuits regulating  
256 appetitive vs aversive memory encoding and processing are separate and if not, how much they  
257 overlap. One possibility is that inverted activity patterns of the same circuits may regulate the  
258 balance between aversive and appetitive emotions and prevent memory interference and  
259 distortion. If so, what is the role of sleep in shaping this balance?

260 Emotional experiences affect the quality and structure of sleep and likely its “mnemonic content”  
261 related to memory consolidation as well. In turn, sleep structure and quality affect emotional  
262 perception and learning. This reciprocal influence could be turning into a vicious circle in the case  
263 of PTSD, where sleep disturbances, long considered a consequence of the disease, are now

264 regarded as potentially causing or at least reinforcing it. Actually, it is yet unclear if and how normal  
265 sleep-dependent aversive memory consolidation processes are “hijacked” to lead to PTSD. Should  
266 PTSD be considered an “over-consolidation” or rather an impaired consolidation of the traumatic  
267 memory? Is it an inability to consolidate extinction and/or new safety memories or does the  
268 installment of PTSD involve dysfunctions of longer-term emotional regulatory processes  
269 independent of early consolidation phases?

270 Memory processing during sleep has essentially been studied, at least in rodents, through the lens  
271 of hippocampus-dependent spatial memory and its consolidation *via* the hippocampo-cortical  
272 dialogue. In particular, the effect of REM and non-REM sleep oscillations on hippocampal and  
273 cortical synaptic homeostasis and plasticity is relatively well-known (Puentes-Mestril et al.  
274 2019) but overall, little attention has been given to extra-hippocampal features of the engram.  
275 Meanwhile, state of the art optogenetic engram studies have uncovered many mechanisms related  
276 to the acquisition and retrieval of emotional associative memories, but little attention was given to  
277 the consolidation phase and sleep-related processing of these emotional engrams. In the future,  
278 combining knowledge and techniques from these two traditionally separate fields of research will  
279 be key in furthering our understanding sleep-dependent emotional processing. Indeed, we now  
280 need a thorough descriptive work of sleep physiology in all the brain areas of the emotion-  
281 processing network to be able to produce or refine hypotheses for separate or coalescing  
282 mechanisms sustaining emotional regulation and emotional memory. These hypotheses can then  
283 be tested in increasingly refined ways using closed loop systems combined with the  
284 tagging/reactivation systems developed in engram studies. This will allow the manipulation of  
285 emotional engrams during specific sleep stages or sleep oscillations in real time in order to further  
286 explore the sleep-specific dynamics of emotional engrams.

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290 During fear conditioning, animals learn to associate an initially neutral conditioned stimulus (CS,  
 291 here a context) with a mild electric shock (an unconditioned stimulus, US). In rodents, when the  
 292 CS is the context (contextual fear conditioning: CFC), the acquisition of the CS-US association  
 293 requires both the hippocampus and the amygdala. When the CS is a simple tone (cued fear  
 294 conditioning), the hippocampus is not necessary. Following CFC acquisition and consolidation, the  
 295 sole presentation of the CS alone is able to trigger a fear response (such as freezing), used as a  
 296 measure for the memory of the CS-US association during retrieval. Retrieval reactivates the  
 297 consolidated memory trace and destabilizes the original memory, which is then restabilized  
 298 through reconsolidation. Extinction is evoked by the repeated exposure of animals to the CS  
 299 (context or tone) without further exposure to the electric shock, leading to a loss of the conditioned  
 300 fear over time ("no freezing"). Most effective treatments for trauma and stressor-related disorders  
 301 rely on this process of extinction, called exposure therapy in humans. As extinction is considered  
 302 as new learning, its stabilization also requires subsequent consolidation. Many studies have used  
 303 the canonical contextual fear conditioning paradigm to study hippocampal memory processing and  
 304 network reorganization but without focusing on the emotional aspect of these memories. In these  
 305 cases, the fear response (freezing) was only used as a behavioral readout for the impaired or  
 306 successful consolidation of the hippocampal engram. Further studies, including those using  
 307 classical (like tone) fear conditioning will be necessary to determine how engrams are modified  
 308 during sleep in other brain regions involved in emotional memories.

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## 318 **Annotations for references**

### 319 **Outstanding interest:**

#### 320 **Boyce 2016**

321 This seminal paper provides the first causal proof that REM sleep theta oscillations are  
322 instrumental for emotional memory consolidation. Indeed, their experiments show that  
323 attenuating the theta rhythm in the HPC by selectively inhibiting the medial septum impairs  
324 contextual fear memory if the inhibition takes place during REM, but not during non-REM sleep.

#### 325 **Trouche 2016**

326 This study reveals that recoding a cocaine-place memory engram in HPC can alleviate  
327 associated maladaptive behavior. Silencing HPC neuronal representation of a place associated  
328 with cocaine revokes drug-induced spatial preference and allows new HPC engrams unrelated to  
329 the emotionally relevant location to emerge.

#### 330 **Girardeau 2017**

331 This study shows that in the non-REM sleep after learning the location of an aversive air-puff,  
332 BLA and HPC neuronal populations engage in cross-structure reactivation of the coordinate firing  
333 that had developed during the task. These reactivations may represent a joint place-threat  
334 representation formed cooperatively by the BLA and HPC supporting aversive memory  
335 consolidation.

#### 336 **Ghandour 2019**

337 The activity of contextual fear memory engram cells in the HPC was visualized using calcium  
338 imaging. In particular, this paper reveals that neurons that are part of the emotional memory  
339 engram show higher repetitive patterns that are likely involved in memory consolidation since  
340 they exhibit high reactivation in the subsequent post-learning sleep and during memory  
341 retrieval.

#### 342 **Izawa 2019**

343 This recent work proposes a circuit that may be implicated in memory processing during REM  
344 sleep. The authors show that melanin concentrating hormone-producing neurons of the  
345 hypothalamus project to the HPC and their inhibition during REM sleep impairs contextual fear  
346 memory consolidation.

347 **Special interest:**

348 **Kitamura 2017**

349 The paper provides strong evidence supporting the core of classic memory consolidation theory.  
350 At early timepoints after fear conditioning, entorhinal inputs activate BLA engram neurons while  
351 at later consolidation stages mPFC drives BLA engram cells. Therefore, emotional memory  
352 consolidation reorganizes the engram, in particular its extra-amygdalar components.

353 **Vetere 2017**

354 In this study, the authors perform a brain-wide functional interrogation of the neural circuits  
355 activated by emotional learning and show that contextual fear conditioning recruits a wide range  
356 of interconnected hub regions critical to fear memory consolidation.

357 **Rosier 2018**

358 This study demonstrates that REM sleep deprivation impairs remote contextual fear memory  
359 consolidation. Moreover, immediate early gene expression analysis as an indirect marker  
360 of neuronal activity during the retrieval of remote contextual fear memory shows that REM sleep  
361 deprivation is associated with a decrease of the activation of the PFC while the activation is  
362 enhanced in the HPC, BLA, and other regions of the PFC.

363 **Dejean 2016**

364 This is among the first studies to propose a temporal coding mechanism based on the neural  
365 synchronization of neural populations sustaining fear behavior regulation (but, among recent  
366 works, see also Davis et al. 2017).

367 **Ognjanovski 2018**

368 In this paper the authors show that both the inhibition of parvalbumin-expressing interneurons  
369 (PV+) of the HPC during post-learning sleep and sleep deprivation impair synchronous  
370 oscillations in the HPC and contextual fear memory consolidation.  
371 Conversely, rhythmic activation of HPC PV+ interneurons after learning increases HPC  
372 synchrony, counterbalancing the impairment of fear memory caused by sleep deprivation.

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