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

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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 among 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 versus non-REM sleep that underpin emotional regulation and memory consolidation, as well as on distinguishing between these two tightly linked cognitive processes.

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## 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 [1], and at least two cognitive processes have been critically linked to sleep. The first one is memory consolidation [2], that is, the gradual strengthening of memories over time. The second is emotional regulation, allowing for the maintenance of an appropriate level of reactivity to emotional situations (let he who has never experienced irritability or even outbursts of rage/tears when sleep-deprived cast the first pillow). The intensity and vividness of emotions during dreams have also always been a subject of great fascination in art (Figure 1) and conversation in everyday life, driving early studies on the link among dreams, sleep, and emotions in neuroscience.

Emotions can strengthen memories: we remember events that carried strong positive or negative emotional weight better and more vividly. Sometimes we even re-experience these emotions when exposed to reminders of the event, such as the context. For instance, you will feel fear when walking down a street where you were bitten by a dog, a phenomenon similar to Pavlovian conditioning. These associative memories, although critical to avoid danger and promoting survival, can become maladaptive in patients suffering from trauma and stressor-related disorders such as post-traumatic stress disorder (PTSD), a mental condition associated with sleep disturbances and severe nightmares [3]. In short, sleep seems to be pivotal in 'emotional processing', an umbrella term used to encapsulate i) emotional associative memory consolidation, ii) the modulation of episodic memory by emotions and iii) emotional regulation [4].

Sleep itself is composed of several different stages associated with distinct physiological features occurring in cycles throughout the night. Although it is an oversimplification, a main distinction can be made between rapid eye movement (REM) sleep and non-REM sleep. REM sleep is also called paradoxical sleep because the electroencephalogram (EEG, or local field potential, LFP, for intracranial recordings) is very similar to wakefulness, but associated with complete muscle atonia. Non-REM sleep encompasses several substages during which the non-REM characteristic rhythms (spindles, K-complexes, slow oscillations, hippocampal ripples) occur in varying proportions. In humans, the role of sleep in emotional processing has been extensively investigated using a wide variety of approaches. Typically, studies measure emotional reactivity and/or learning and correlate their related neural activity (fMRI, EEG) with sleep features such as the relative quantity of REM and non-REM sleep, the structure, quality, and quantity of sleep, EEG features (sleep oscillations) or sleep manipulations

**Figure 1**


Johann Heinrich Füssli - The Nightmare, oil on canvas, 1781.

(sleep deprivation). For example, hearing one's own recorded voice butchering a karaoke song triggers feelings of shame and embarrassment associated with an fMRI activation of the amygdala, a core structure for the processing of emotions. Normal REM sleep, but not fractioned REM sleep, leads to a decrease in amygdala reactivity upon hearing the recording the following day [5]. The effect also correlates with the spindle-rich period preceding REM sleep recorded by EEG, hinting at the importance of transition periods, and potentially the alternation between sleep stages. There are a number of excellent reviews exposing the current landscape of research about the role of sleep in emotional processing in humans [1,2,4,6].

While it appears from the human literature that sleep is indeed crucial to emotional processing, no clear consensus has yet emerged about the respective roles of REM or non-REM sleep. It is also still unclear whether emotional associative memory, the influence of emotions on memory, and emotional regulation are distinct or overlapping processes associated with specific sleep stages or rhythms. To gain further insights into the neural bases that sustain the role of sleep in emotional processing, one has to turn to model organisms where the range of available technologies and experimental designs allows the observation and manipulation of neural networks with a better spatial and temporal resolution. In particular, the advent of optogenetic tools for real-time close-loop manipulation has enabled the activation or inhibition of neural responses during specific sleep events (short REM sleep episodes or specific oscillations) detected 'on-the-fly' [7,8••,9]. Here, we will provide an overview of the recent developments in rodent research about the role of sleep in emotional processing at the systems level (cellular and molecular mechanisms for emotional plasticity are beyond the scope of this review), with a particular focus on aversive and appetitive associative learning.

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

Memories are thought to be stored and retrieved within specific neuronal ensembles called 'engrams' [10,11], which are initially recruited during acquisition. Distributed engram ensembles for emotional memory encompass several brain regions including the hippocampus, the prefrontal cortex and the amygdala. In particular, the basolateral amygdala (BLA) is where the emotional valence of a stimulus (aversive or appetitive; [12,13]) is associated with a sensory and/or contextual stimulus in conditioning paradigms [14]. The optogenetic activation of engram cells in the hippocampus, cortex or BLA triggers emotional memory retrieval, while their silencing blocks it [11,14,15••,16]. Most engram studies explore

how events are initially encoded into engrams, and how memory retrieval relies on the same or modified engram at various timepoints after encoding. This suggests the existence of 'off-line' consolidation and maturation processes that change the structure of the brain-wide engram over time between encoding and retrieval. For example, Kitamura *et al.* [17•] used complex engram tagging, inhibition and reactivation at remote and recent timepoints after learning in mice to show that immature engram ensembles are formed at the time of the contextual fear acquisition (Figure 2) in the hippocampus (HPC), BLA and medial prefrontal cortex (mPFC). The mPFC part of the engram becomes functional and is required only during remote recall. Indeed, a reorganization of the emotional memory network gradually takes place throughout the 12–30 day period following acquisition [18•].

During this consolidation phase between acquisition and retrieval, animals cycle through different behavioral states, including NREM and REM sleep. For example, REM sleep deprivation after contextual fear conditioning (Figure 2) impairs remote, but not recent, emotional memory and alters the network activated during remote retrieval [19•], suggesting that early sleep phases after fear acquisition could 'set up' the network 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 [20]. 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 [21,22••,23]. Choi *et al.* [21] 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 [22••]. Reactivation during the post-learning sleep period could sustain the strengthening of existing synapses between engram cells.

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

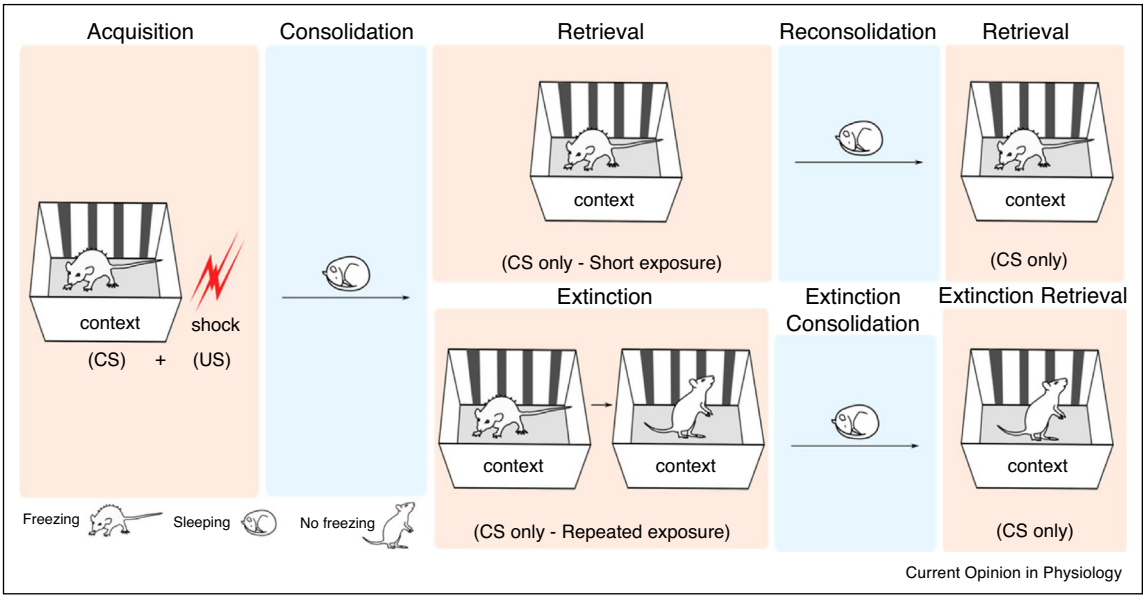
Memory consolidation during sleep has been extensively studied in rodents through the lens of replay of place cells in the hippocampus. Indeed, during Non-REM sleep ripples, entire sequences of place cells are reactivated: the neural activity of the previous wakefulness epoch is reinstated during the subsequent sleep epoch ('replay'; see Foster [24] 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 [25,26], establishing the crucial role of ripples and replay in spatial memory consolidation. Hippocampal reactivations during sleep are increased [27,28] and prolonged [29] 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 learning promotes subsequent ripple-associated hippocampal reactivations [28,30].

The hippocampal representation of space itself is also modulated by emotions during the memory encoding phase. Indeed, emotional contingencies directly influence place-cell firing [31–34]. A specific non-place, reward-coding population was even recently described in the hippocampus [35]. Therefore, the effects of emotions on memory are likely initiated during training and prolonged during consolidation. Interestingly, pharmacological or optogenetic activation/inhibition of the BLA following training in rats bidirectionally modulates spatial aversive memory consolidation [36,37]. However, it is still unknown how aversive (as opposed to reward-related) stimuli influence subsequent replay during sleep.

Interestingly, pairing the activation during non-REM sleep of one specific place cell with a pleasurable stimulation of the medial forebrain bundle (MFB) in mice induces an artificial place preference after sleep for the location associated with the place cell [38]. This suggests that the emotional valence of spatial representation can be updated throughout memory consolidation during sleep. Similarly, during wakefulness the emotional valence of a given stimulus is constantly updated by experience. In Pavlovian conditioning protocols, the repeated exposure to a stimulus or a context (the conditioned stimulus, CS) previously paired with an aversive or appetitive unconditioned stimulus (US) induces extinction of the behavior associated with the US (Figure 2). Importantly, during sleep, the presentation of the CS alone has a different effect. Indeed, reinstating an olfactory CS during non-REM sleep improves an odor-shock associative memory ([39,40]; but see Ref. [41]), whereas the same reinstatement during wakefulness triggers extinction [39].

In short, activating part of a memory trace during sleep might be recruiting the complementary part of the engram through cross-structure pattern completion that would reinforce the associative memory. Indeed, cross-structure reactivations have been described between the

**Figure 2**




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

rat hippocampus and basolateral amygdala during non-REM sleep following an aversive spatial learning task [42••]. These joint reactivations occurred preferentially during hippocampal ripples, and were biased towards the aversive locations. Although the temporality of the hippocampus-BLA reactivations remains to be assessed, reactivations of the spatial context during ripples in the hippocampus might trigger the recruitment of the amygdala part of the engram, thereby reinforcing the connections between the two. In fact, this can be done artificially during wakefulness by activating separately tagged hippocampal 'spatial' and BLA 'shock' engrams together to create a *de novo* aversive associative memory [16]. On a side note, the activity of amygdalar neurons in monkeys learning an appetitive or aversive tone-odor pairing reverberates during the post-trial epochs [43], suggesting the existence of 'replay-like' mechanisms in the BLA during quiet wakefulness at least.

Coordinated activation between neurons of the hippocampus and ventral striatum has also been reported during the acquisition of place-reward tasks [44], and the following NREM (but not REM) sleep epoch. These reactivations occur during ripples and the hippocampus tends to lead the reactivations [45–47]. Dopaminergic VTA neurons that have reward or aversive stimulus-related activity also reactivate during sleep [48]; however, VTA replay in coordination with hippocampal place-cells and ripples is restricted to quiet wakefulness and does not occur during NREM sleep *per se* [49].

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

The main electrophysiological characteristic of REM sleep identified so far is the presence of strong hippocampal theta oscillations. Oscillations in general are believed to coordinate neuronal firing between distant structures, including the hippocampus-amygdala-prefrontal cortex network that is crucial to emotional memory [50–54,55•,56,57]. In a seminal paper, Popa *et al.* [50] showed that the coherence at theta frequency between the BLA and the hippocampus, as well as between the BLA and the medial prefrontal cortex, was increased during REM sleep following training on auditory fear conditioning compared to the preceding

REM sleep. Moreover, the performance during retrieval 24 hour later correlated with these changes in coherence. More recently, Boyce *et al.* [8••] used optogenetics to silence GABAergic neurons of the medial septum, the major theta-generator, specifically during REM sleep following several behavioral tasks in mice. Effectively shutting down theta oscillations during REM sleep, they showed that performance is impaired in the novel object recognition task (hippocampus-dependent), and in contextual fear conditioning (Figure 2; both hippocampus and BLA-dependent). Interestingly, there is no impairment in conditioning to the auditory cue, which relies on the BLA, but is hippocampus-independent. Similarly, post-training pharmacological blockade of gap-junctions, which impairs theta oscillations, prevents the consolidation of contextual, but not cued, fear conditioning [58], although the manipulation here was not restricted to REM sleep. Theta oscillations during REM sleep are therefore a good candidate for offline coordinated activity related to emotional processing [59,60]. REM sleep is modified after both appetitive and aversive training [59,61], while total and selective REM sleep deprivation after training impairs emotional memory consolidation and prevents the related network reorganization [19•,62,63,64•].

The control of REM sleep (transitions from NREM to REM, REM to wake, duration and quantity of REM sleep episodes) involves a number of structures and neurons, the exquisite complexity of which is being gradually revealed (reviewed in Ref. [65]). REM sleep control is traditionally studied separately from REM sleep functions, including emotional processing. Nevertheless, activating REM-promoting melanin concentrating hormone–producing (MCH) neurons in the hypothalamus impairs contextual (but once again, not cued) fear conditioning, while inhibiting them promotes contextual fear memory consolidation [66••]. However, it is yet unknown how MCH neurons manipulations affect REM sleep theta oscillations and hippocampal neural activity during REM. This paper is also conceptually interesting because it suggests that the circuits controlling REM sleep and those underlying its mnemonic and emotional functions could be widely overlapping. In that same line of thought, pontine waves (P-waves) originating from the brainstem (which is instrumental for sleep-wake regulation), occur primarily during REM sleep and were shown to coordinate with theta oscillations [67]. P-wave density also correlates with the successful extinction of contextual fear-conditioning [68]. Overall, this literature suggests that theta oscillations during REM sleep might be involved in the consolidation of the contextual information, rather than the *association* between the shock and contextual information. This corpus of findings is at odds with the fact that neither hippocampal nor hippocampus-amygdala replay has been reliably shown during REM sleep [42••,69], and that typically REM sleep has been viewed as a stage beneficial to emotional processing [59] rather than spatial memory. Further work is needed to resolve this paradox.

## Open questions, challenges and future directions

The title 'the role of sleep in emotional processing' hides a nebulous, multidimensional field of research where isolated bursts of knowledge, some reviewed here, are still in need of a unifying theory, if there can be one. Indeed, sleep itself is divided into several distinct stages, defined differently across species [70] and under the control of an immensely complex network of structures involving a delicate balance of neurotransmitters and hormones that is not yet fully understood [71]. In addition, 'emotional processing' covers several concepts including emotional regulation, associative memory (aversive and appetitive conditioning), episodic memories associated with an emotional weight and the modulation of memories by emotions.

From the current state of knowledge, one emerging hypothesis is that non-REM sleep is involved in consolidating contextual associative memories via ripple-related coordination with other structures involved in appetitive and aversive memories. REM sleep, in contrast, could have different roles depending on the brain structure and type of memory. Because most studies show an effect on contextual, but not cued, fear conditioning, REM could selectively influence the hippocampal part of the emotional engram via theta oscillations, while having a yet undefined regulatory role on amygdala function and potentially other non-neocortical structures. It is also possible that the 'alternation' between non-REM and REM sleep is required for either emotional regulation and/or emotional memory consolidation [72].

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

Emotional experiences affect the quality and structure of sleep and likely its 'mnemonic content' related to memory consolidation as well. In turn, sleep structure and quality affect emotional perception and learning. This reciprocal influence could be turning into a vicious circle in the case of PTSD, where sleep disturbances, long considered a consequence of the disease, are now regarded as potentially causing or at least reinforcing it.

Actually, it is yet unclear whether and how normal sleep-dependent aversive memory consolidation processes are 'hijacked' to lead to PTSD. Should PTSD be considered an 'over-consolidation' or rather an impaired consolidation of the traumatic memory? Is it an inability to consolidate extinction and/or new safety memories or does the installment of PTSD involve dysfunctions of longer-term emotional regulatory processes independent of early consolidation phases?

Memory processing during sleep has essentially been studied, at least in rodents, through the lens of hippocampus-dependent spatial memory and its consolidation via the hippocampo-cortical dialogue. In particular, the effect of REM and non-REM sleep oscillations on hippocampal and cortical synaptic homeostasis and plasticity is relatively well-known [72] but overall, little attention has been given to extra-hippocampal features of the engram. Meanwhile, state of the art optogenetic engram studies have uncovered many mechanisms related to the acquisition and retrieval of emotional associative memories, but little attention was given to the consolidation phase and sleep-related processing of these emotional engrams. In the future, combining knowledge and techniques from these two traditionally separate fields of research will be key in furthering our understanding sleep-dependent emotional processing. Indeed, we now need a thorough descriptive work of sleep physiology in all the brain areas of the emotion-processing network to be able to produce or refine hypotheses for separate or coalescing mechanisms sustaining emotional regulation and emotional memory. These hypotheses can then be tested in increasingly refined ways using closed loop systems combined with the tagging/reactivation systems developed in engram studies. This will allow the manipulation of emotional engrams during specific sleep stages or sleep oscillations in real time in order to further explore the sleep-specific dynamics of emotional engrams.

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## Conflict of interest statement

Nothing declared.

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