



HAL
open science

The role of the hippocampus in the consolidation of emotional memories during sleep

Éléonore Pronier, Juan Facundo Morici, Gabrielle Girardeau

► **To cite this version:**

Éléonore Pronier, Juan Facundo Morici, Gabrielle Girardeau. The role of the hippocampus in the consolidation of emotional memories during sleep. Trends in Neurosciences, In press, 10.1016/j.tins.2023.08.003 . hal-04210129

HAL Id: hal-04210129

<https://hal.sorbonne-universite.fr/hal-04210129>

Submitted on 18 Sep 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **The role of the hippocampus in the consolidation**
2 **of emotional memories during sleep**

3 Éléonore Pronier¹, Juan Facundo Morici¹, Gabrielle Girardeau^{1*}

4 ¹Institut du Fer à Moulin, Inserm U1270, Sorbonne Université.

5 *Correspondance: gabrielle.girardeau@inserm.fr (G. Girardeau)

6 **Keywords**

7 Oscillations; Reactivation; REM sleep; rodent; consolidation; engram; sharp-wave ripples

8 **Abstract**

9 Episodic memory relies on the hippocampus, a heterogeneous brain region with distinct functions.
10 Spatial representations in the dorsal hippocampus are crucial for contextual memory, while the
11 ventral hippocampus is more involved in emotional processing. Here, we review the literature in
12 rodents highlighting the anatomical and functional properties of the hippocampus along its dorso-
13 ventral axis that underlie its role in contextual and emotional memory encoding, consolidation, and
14 retrieval. We propose that the coordination between the dorsal and ventral hippocampus through
15 theta oscillations during REM sleep, and through sharp-wave ripples during non-REM sleep, might
16 facilitate the transfer of contextual information for integration with valence-related processing in
17 other structures of the network. Further investigation into the physiology of the ventral
18 hippocampus and its connections with other brain areas is needed to deepen the current
19 understanding of emotional memory consolidation during sleep.

20 **Main Text**

21 **The hippocampus and spatial and emotional memory consolidation during sleep**

22 Sleep is a physiological state present throughout the entire animal kingdom. In mammals, a
23 characteristic feature of sleep is a reversible loss of consciousness associated with behavioral
24 quiescence. This vulnerable state plays a vital role in the proper functioning of various organs,
25 particularly the brain. Sleep deprivation notably impairs two interconnected cognitive processes:
26 memory consolidation, i.e. the gradual strengthening of memories over time, and emotional
27 processing [1]. Emotions have the potential to enhance memory formation, as experiences that
28 evoke positive or negative emotional responses are more effectively remembered [2]. Specific
29 contexts can also be associated with emotions, forming direct associations so that the emotion is re-
30 experienced when exposed to the same context, a phenomenon modeled in rodents with contextual

31 fear conditioning. Emotions are characterized by their valence, which can range from negative to
32 positive, and by their intensity, which will in turn influence the arousal level triggered by the
33 emotion. Both valence and intensity will influence the processing of the emotion and its effect on
34 memory.. Extensive research in rodents has focused on studying how the physiology of the dorsal
35 hippocampus (dHPC), a central structure for contextual memory, contributes to the encoding,
36 consolidation, and retrieval of spatial memories during both wakefulness and sleep. The ventral
37 hippocampus (vHPC) is considered functionally distinct from the dHPC, and a large body of selective
38 lesions and pharmacological inactivation studies established its role in emotional processing,
39 especially stress-, fear-, and anxiety-related behaviors [3–9]. Here, we review the rodent literature to
40 first, compare the known spatial and emotional features of the dorsal and ventral hippocampus. We
41 then discuss evidence supporting the notion that the interactions between the hippocampus and
42 other core valence-processing structures, such as the basolateral amygdala (BLA), nucleus
43 accumbens (NAc), anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC), are crucial
44 for the processing of spatial and emotional information during sleep. Notably, we argue for a
45 potential role of the vHPC as a central hub for integrating context and valence information,
46 contributing to emotional memory acquisition and retrieval, as well as consolidation during sleep.
47 Investigating well-known mechanisms of the dHPC like neural reactivation, non-REM sleep sharp-
48 wave ripples, and REM sleep theta oscillation in the vHPC in the context of emotional memory
49 consolidation and exploring how the valence of an experience modulates dorso-ventral coordination
50 during sleep will deepen current understanding of how contextual information is processed in
51 parallel or convergence across the hippocampus dorso-ventral axis and associated with emotional
52 information to consolidate the memory of emotional experiences.

53 **Spatial and emotional neural representations along the hippocampus dorso-ventral axis**

54 The hippocampus contains place cells that selectively activate at particular locations of an
55 environment, called the place field [10,11]. Altogether, hippocampal place cells form cognitive maps
56 [12,13] believed to sustain spatial learning. The exposure to a completely different environment can
57 lead to drastic reconfiguration of the hippocampal cognitive map, a process referred to as global
58 remapping, but more moderate changes in the environment, like spatial ‘stretching’, re-shaping, and
59 adding or removing sensory cues lead to more subtle changes in the spatial representation: in some
60 cases, place cells only change their firing rate (referred to as rate remapping), and in other cases a
61 subset of cells changes the location of their place-fields (referred to as partial remapping; see [14]
62 for review). In the dHPC, spatial representations can be modulated by the emotional valence of an
63 experience. For instance, the introduction or removal of an aversive footshock in an environment,

64 such as in contextual fear conditioning and extinction, respectively, triggers remapping [15–17].
65 Place fields tend to relocate towards locations associated with positive valence (or reward), referred
66 to as “goal-directed remapping”, or towards locations associated with negative valence (e.g. due to a
67 air puff), leading to a higher density of place fields around emotionally salient zones [18,19]. A
68 subset of dHPC cells activates specifically at reward sites, independently of their location, thus
69 directly encoding positive valence independently of space (“reward cells”, [20]). In addition, there
70 are dHPC cells specifically active during freezing, a typical fear-related behavior [17].
71 Representations in the dHPC are therefore mostly spatial but can adapt to integrate valence-related
72 information.

73 Compared to the dorsal part of the hippocampus, the vHPC contains a smaller number of place cells
74 with larger place fields [21–23]. During wakefulness, the hippocampal local field potential (LFP)
75 displays 6-12Hz theta oscillations, and place cell activity occurs at gradually earlier phases of theta as
76 the animal crosses the place field. This mechanism, called “phase precession” [24], contributes to
77 the organization of place cell activity into “theta-sequences” at a timescale compatible with
78 plasticity [25,26]. Phase precession is slower in the vHPC [22]. During spatial navigation, ventral
79 neurons are less theta-modulated than dorsal ones, but theta power is also overall lower in the vHPC
80 [27]. In the dHPC, but not in the vHPC, theta amplitude and frequency correlate with features of the
81 animal’s locomotion (e.g. speed and acceleration) [28,29]. The changes along the dorso-ventral axis
82 at the single neuron level pervade into the population dynamics, with a reduced dimensionality in
83 the vHPC [30] corroborating a decreased spatial accuracy (but see [23]). Paralleling this decrease in
84 spatial features (Fig. 1), there is an increase in valence-related activity in the vHPC: the number of
85 place cells remapping towards rewards and neurons directly encoding reward increases from the
86 dorsal to the intermediate hippocampus [31,32], and the vHPC displays specific neuronal patterns in
87 response to anxiogenic vs. safe environments, or close to rewards [33–35]. vHPC inhibition is
88 anxiolytic [34], and a reduced vHPC activation was observed in mice resilient to stress [36]. There are
89 shock-responsive cells in the vHPC [37], and different subpopulations respond to aversive stimuli vs.
90 reward [38,39].

91 In ethological contexts, it is crucial to associate specific places with salient emotional experiences, to
92 find food or stay hyper-vigilant in a zone where a predator was previously encountered. It is
93 therefore difficult to disambiguate spatial and emotional learning. The vast majority of studies on
94 spatial coding and memory use rewards to stimulate exploration, making them inherently positively
95 valenced. Still, it is possible to design experiments to reveal non-spatial emotional properties of the
96 hippocampus. For example, two recent studies in head-fixed animals using odors associated with

97 reward or punishment found that the vHPC was more responsive to the predicted positive or
98 negative outcome of the odor [40,41]. vHPC neurons also respond to the sound stimulus predicting
99 the shock during cued fear extinction [42]. Thus, both the dorsal and ventral hippocampus display a
100 mix of valence-related and spatial features, but the representations are heavily biased towards
101 space in the dHPC and towards valence and salience in the vHPC, sustaining the functional gradient
102 from spatial to emotional along the dorso-ventral axis.

103 **Hippocampal representations support the retrieval of emotional memories**

104 The term ‘engram’ has been often used to indicate the population of neurons that constitute the
105 physical trace of a memory in the brain and whose activation supports the retrieval of this memory.
106 Can hippocampal space and valence representations be seen as engrams for emotional memories?
107 In other words, can the activation of dHPC or vHPC representations trigger emotion-related
108 behaviors, effectively constituting the support of emotional memory recall? A series of studies
109 leveraged tagging and optogenetics methods to address this question. In the dHPC, optogenetic
110 activation of neuronal ensembles previously associated with a positive (reward) or negative
111 (footshock) environment is sufficient to trigger the behavior related to the emotional experience (e.g
112 licking for reward or freezing) in another, neutral environment [43, 44]. These associations between
113 the valence and the spatial representation can also be artificially manipulated : for example, when the
114 opto- activation of a neutral spatial representation is paired with a footshock, the activation of this
115 initially neutral representation subsequently triggers freezing in an neutral environment [45]. The
116 associations between hippocampal neurons representing a specific context and an emotional
117 valence, can also be reversed from positive to negative, and a freezing response in a negatively
118 valenced environment can be reduced by the opto-activation of a competitive engram associated
119 with a positive valence [46, 47]. Finally, extinction training, i.e. reexposing an animal to a
120 conditioned stimulus without any threat, suppresses the activation of a dHPC “fear” engram while
121 activating a new “extinction” engram: manipulating those distinct engrams directly impacts
122 extinction and relapse of fear memory [48]. vHPC engram studies are still sparse, but seem to
123 indicate that the activation of ventral hippocampus engrams can also drive valence-related
124 behaviors: artificially reactivating vHPC cells active during encoding enhances behavioral expression
125 of fear or reward place preference during retrieval, through interactions with the BLA [49]. Hence,
126 activation of either the dHPC or vHPC engrams can sustain the recall of contextualized emotional
127 memories, likely through the recruitment of a larger engram spanning other valence-related
128 structures. The limited connectivity of the dHPC and extended connectivity of the vHPC (see Box 1)

129 places the vHPC in a strategic position for the transmission and integration of dHPC contextual inf
130 ormation with valence information.

131 **The vHPC selectively receives and routes information from/to other valence-processing structures**

132 The valence-related activity of the vHPC is sustained by vHPC's direct connections with other brain
133 regions involved in valence processing. Different neuronal pathways sustain distinct behaviors. The
134 pathways between the vHPC, basal amygdala (BA) and BLA, mPFC, ACC, and NAc have received
135 particular attention. Manipulating vHPC inputs to BA or BLA in mice modulates contextual fear
136 response [50,51], without affecting anxiety-like behaviors, potentially sustained by another pathway
137 including the lateral hypothalamus [37], and the medial prefrontal cortex [52]. In the vHPC, the
138 neurons responding to shock during contextual fear conditioning preferentially project to BLA [37].
139 Contextual fear conditioning induces a strengthening of vHPC-BA synapses, especially for a subset of
140 BA neurons that receive monosynaptic inputs from context-responding vHPC cells [53]. These vHPC
141 inputs to the BA are necessary for contextual fear retrieval [54]. The inputs from vHPC to the NAc
142 promote susceptibility to chronic stress [36], but also mediate cocaine-induced place preference and
143 reward-oriented behavior, potentially linking a spatial-emotional joint engram in the vHPC with a
144 valence engram in the NAc [35,55]. Inputs from the vHPC to the mPFC modulate the acquisition and
145 retrieval of fear and fear extinction memory [56–58], probably through the transfer of contextual
146 information. vHPC to mPFC inputs are also involved in the bi-directional modulation of anxiety-
147 related behavior in the absence of learning [52,59]. Finally, parallel vHPC to lateral septum
148 projections are involved in approach/avoidance behavior [60].

149 The vHPC sends projections to multiple valence-related structures along segregated paths, but also
150 receives inputs from these structures. Manipulating BLA inputs to the vHPC in mice modulates
151 anxiety-like behaviors, depressive-like behaviors, and fear extinction [61–63]. Post-training
152 manipulation of the BLA inputs to the vHPC modulates aversive memory consolidation [64,65]. The
153 BLA neurons projecting to the vHPC encode positive and negative valence in the same proportion
154 [66]. The vHPC was also shown to be important for contextual fear generalization, a form of long-
155 term memory, through its connections with the ACC [67,68]. Using tracing and selective optogenetic
156 manipulations, these studies have established the vHPC as a strategic outpost for the circulation of
157 valence information within a larger network during wakefulness. Sleep is crucial for spatial memory
158 consolidation, but the mechanisms underlying the consolidation of emotional memory along the
159 anatomo-functional pathways described in this section are mostly unknown.

160 **The reactivation of hippocampal representations during sleep sustains memory consolidation**

161 Memory consolidation is believed to occur partially during sleep through the “off-line” activation of
162 patterns of neural activity previously elicited during learning, a phenomenon referred to as
163 reactivation. Early reactivation studies in rats described that the firing rates or pairwise correlated
164 activity observed during wakefulness in the dHPC were maintained during the following non-REM
165 (NREM) sleep epoch [69,70]. It is now known that the temporal order of place cell firing can be
166 conserved during reactivation, replaying entire trajectories during NREM following exploration
167 [71,72]; this type of sequence reactivation is called “replay” [73–75]. Hippocampal reactivation
168 preferentially occurs during hippocampal sharp wave-ripple complexes (SWRs) generated by the
169 synchronous, spontaneous activation of CA3 pyramidal neurons propagating to the CA1 region [76].
170 SWRs are believed to enable a decrease in the synaptic strength of irrelevant neuronal connection
171 by promoting network long-term depression (LTD;[77]), and the strengthening of relevant neuronal
172 connections through selective long-term potentiation (LT;[78]), effectively enhancing the signal-to-
173 noise ratio and therefore supporting memory consolidation [79]. In rats, the blockade of dHPC SWRs
174 during post-learning NREM, which concomitantly silences hippocampal activity and therefore the
175 associated reactivation, impairs spatial memory consolidation in rats [80,81]. On the contrary, the
176 selective sparing of reactivation associated with an environment by suppressing all other
177 synchronized events including reactivation of a second environment induces a learning impairment
178 restricted to the suppressed environment [83]. The indirect suppression of dHPC SWRs during NREM
179 sleep also impairs contextual fear conditioning in mice [82]. . NREM sleep SWRs and reactivation in
180 the dHPC thus sustain spatial memory consolidation.

181 How does emotional valence influence reactivations? During sleep ripples, stimulating dopaminergic
182 inputs to the dHPC increases pairwise reactivation [84], suggesting an influence of valence or
183 salience on sleep replay [85]. Artificially pairing place-cell activity during sleep with middle forebrain
184 bundle (MFB) stimulations, thought to be intrinsically pleasurable through the activation of
185 dopaminergic fibers, induces subsequent reward-related behavior toward the associated place field
186 locations [86]. Thus, the activation of the dopaminergic system during sleep directly influences
187 spatial memory consolidation, but the effect of valence on sleep reactivation is likely initiated during
188 the encoding phase, a process conceptualized as “emotional tagging” [87]. Indeed, a study in rats
189 underscored a preferential role of hippocampal replay for the consolidation of large rewards
190 compared to small ones during a 2 hours delay period between acquisition and retrieval [88].
191 Dopamine release is modulated by reward, aversive stimuli, salience, uncertainty, and novelty [89],
192 and mediates hippocampal synaptic potentiation and neuron excitability [90], potentially enhancing
193 the hippocampal representations of relevant locations and influencing the replay content of awake
194 SWRs occurring during non-exploratory states of wakefulness [73,91,92]. Awake ripples and reverse

195 replay are enhanced by the presence of reward [93,94], and awake replay will preferentially
196 represent trajectories leading to a reward [95] (but see [96]). Replay has been detected during the
197 avoidance of a shock zone [97], suggesting that it might sustain aversive memory retrieval. Finally,
198 place cells that remap in a spatial avoidance task increase their participation in awake ripples during
199 training [98], suggesting a link between the integration of aversive elements into the hippocampal
200 representation and its immediate preferential processing. Another parameter to consider is that
201 animals will avoid an aversive zone, and spend more time around rewarded areas, effectively
202 reducing or increasing, respectively, the activity of the corresponding place cells, which could
203 directly affect later reactivation. The acute stress triggered by an aversive experience could also
204 influence reactivation, as suggested by the fact that repeated restraint stress decreases CA1
205 pyramidal activity, but increases participation in SWRs during wake and sleep [99]. Of note, chronic
206 stress might have longer-term deleterious effects on memory, which differ widely from those of
207 acute stress [100].

208 Like the dHPC, the vHPC also displays ripples during non-exploratory wakefulness and NREM sleep.
209 However, it remains unknown whether vHPC ripples are associated with reactivation (see
210 Outstanding Questions). We propose that the vHPC relies on consolidation principles similar to those
211 established in the dHPC for spatial memory consolidation [74], but applied in the vHPC to
212 consolidate valence-related information. To what extent this valence information would be
213 contextualized remains to be established, as well as the mechanisms involving neuromodulatory
214 systems by which valence during an experience will influence later dHPC and vHPC sleep-dependent
215 reactivation.

216 **Neural oscillations coordinate the hippocampus and other valence-processing structures**

217 *Theta oscillations during encoding and retrieval*

218 Various models of contextual emotional learning involve the hippocampus in combination with other
219 valence-related structures. Contextual fear conditioning (CFC) is the canonical model for
220 contextualized aversive memory, i.e. the association of a specific context with an aversive stimulus,
221 usually a footshock, in the context of rodent studies. CFC requires both the dHPC, believed to
222 process the context, and the BLA [101], one of the core structures of the network processing fear
223 and anxiety [102], including fear memory. Conditioning an animal to a simple auditory cue does not
224 appear to require the hippocampus, suggesting that the hippocampus and the BLA interact to
225 integrate aversive with context information. In addition, the mPFC, which has limited connectivity
226 with the dHPC, is involved in the control of the expression of conditioned fear [103]. Observational

227 fear learning (OFC) is a complex behavior that involves context, valence, and social processing.
228 Animals having experienced shocks in a given context exhibit freezing when watching a conspecific
229 experiencing the shock. The initial formation of the memory trace of the context in the dHPC is
230 required and drives the formation of a memory trace in the BLA. A study in mice has shown that the
231 expression of OFC involves the vHPC and BLA [104], and highlights the joint involvement of both the
232 dHPC and vHPC in processing memories involving context and valence, in coordination with other
233 structures of the network, in this case, the BLA [64]. What are the neural mechanisms underlying
234 these interactions? Oscillations are believed to synchronize neural activity within and across
235 structures, and phase-locking (i.e. the firing of neurons at specific phases of the LFP oscillation) is a
236 marker of this synchronization. Within the hippocampus during exploration and movement, theta
237 paces place-cell activity, organizing the neuronal assemblies that will later be reactivated during
238 sleep [25]. The peak and troughs of the theta rhythm are favorable to LTP and LTD, respectively, in
239 awake and anesthetized animals [105–107]. Coordination in the theta band between the dHPC, the
240 amygdala, and the mPFC correlates with the acquisition and retrieval of cued and contextual fear
241 conditioning [108–111]. Of note, however, the theta band as defined in these publications
242 potentially overlapped with the 4-Hz coordinated oscillation between the mPFC and amygdala that
243 was later shown to control the expression of freezing [112,113]. In a study in mice, manipulating
244 theta power in the vHPC was shown to modify the amount of exploration of odor predator-
245 associated zones [114]. In addition, theta coordination between the vHPC and mPFC is increased in
246 anxiogenic environments [115], and mPFC units responding to aversive or safe stimuli in anxiogenic
247 tasks are strongly locked to vHPC theta, but not dHPC theta [116]. In another study, optogenetic
248 stimulation at theta frequency of vHPC inputs to mPFC activity was associated with increased
249 synchronicity between vHPC theta and mPFC spiking activity and enhanced avoidance behavior in
250 the elevated plus-maze [117]. Theta oscillations during wakefulness thus emerge as a key
251 mechanism for the synchronization of dHPC and vHPC with other structures sustaining innate and
252 learned emotional behaviors.

253 *Theta oscillations during REM sleep*

254 Theta oscillations are also a hallmark of REM sleep. Studies in humans point towards a role for REM
255 sleep in emotional memory consolidation ([118], but see [119]). The underlying physiological
256 mechanisms, however, are still largely unknown (see Outstanding questions). Studies in mice and
257 rats have shown that selective REM sleep deprivation or inhibiting theta oscillations during post-
258 learning REM induces contextual memory impairments [120,121]. However, classical, NREM-like
259 dHPC reactivation has not yet been widely found during REM sleep [122], although there are some

260 similarities between awake and REM sleep neuronal patterns [123,124]. Theta power in the dHPC
261 during a REM-sleep episode correlates with an increase in the synchrony and firing rate of pyramidal
262 cells during the SWRs of the following NREM epoch [125], suggesting that REM sleep might initiate
263 plastic changes implemented during NREM sleep. Aversive learning and extinction trigger changes in
264 theta synchronization during REM across the dHPC, vHPC, BLA, and mPFC, especially in the dHPC-BLA
265 coherence and vHPC-LA phase shift [126,127], but in the absence of structured dHPC-BLA
266 reactivation [128]. Hippocampal theta oscillations are traveling waves [129], the propagation of
267 which across the dorso-ventral axis [29] could mediate communication between the dHPC, vHPC,
268 and the rest of the valence-related network through the vHPC connections. Indeed, theta
269 synchronization between the dorsal and ventral hippocampus increases during the retrieval of trace
270 fear conditioning [130]. Thus, further investigation is required to elucidate how changes in the
271 organization of neural activity by REM theta oscillations within the hippocampus and across
272 structures might contribute to the consolidation of experiences of different emotional valence and
273 salience.

274 *SWRs during non-exploratory wakefulness and non-REM sleep*

275 During training on a rewarded spatial task, dorsal and ventral SWRs activate distinct and opposing
276 patterns of NAc spiking. NAc neurons responding to dHPC SWRs show more location and reward-
277 related activity [131], and the coupling between dHPC and NAc neurons encoding a location
278 associated with cocaine administration increases during wakefulness and sleep [132]. This suggests
279 that awake and sleep SPWs originating from the dHPC vs. vHPC could play distinct roles in the
280 integration of space and valence information, supported by the respective anatomical connexions
281 between the dHPC, vHPC, and NAc [133]. Reward-responsive ventral tegmental area (VTA) neurons
282 activate synchronously with dorsal hippocampal reactivation events of appetitive spatial experience
283 during quiet wakefulness [134], and ventral striatum reward-related cells also reactivate in
284 coordination with dHPC place cells during SWRs [135,136], probably primed by the coordination of
285 dHPC-striatal neural activity by theta phase-precession during learning [137]. Thus, interactions
286 between the dHPC and other structures related to reward processing might sustain the
287 consolidation of place-reward associations [86]. On the other end of the valence spectrum, the
288 dHPC-BLA pairwise representation of an aversive experience is reactivated during NREM sleep SWRs
289 [128]. In the absence of direct connections between the dHPC and BLA [138,139], these joint
290 reactivations necessarily involve at least one relay structure, potentially the vHPC. Indeed,
291 inactivating vHPC neurons after training impairs the consolidation of contextual fear memory [140],
292 potentially by impairing the vHPC NREM reactivation of stimulus-related activity which is modulated
293 by BLA inputs [42]. During NREM sleep following fear conditioning, there are also multi-structure

294 reactivations involving the vHPC, BLA, and infralimbic part of the mPFC associated with high-
295 frequency oscillations in vHPC and BLA and modulated by cortical slow waves [141]. Because they
296 propagate along the dorso-ventral axis [142], SWRs are a likely candidate for binding dorsal and
297 ventral hippocampus activity during NREM sleep. There is a progressive decrease in the dorso-
298 ventral coordination of SWRs along the dorso-ventral axis, reaching marginal coordination between
299 the most dorsal and ventral zones (Fig. 2). However, this has only been examined in the absence of
300 previous spatial or emotional learning, and the need for joint consolidation of spatial and valence
301 information could affect dorso-ventral SWR coordination.

302 In the cortex, NREM sleep is characterized by thalamo-cortical spindles and slow oscillations arising
303 from the synchronized alternation of periods of high activity and quiescence in cortical neurons,
304 referred to as “up” and “down” states. Systems consolidation involves a transfer of information from
305 the hippocampus to cortical areas and is mediated by the temporal organization of neural activity by
306 dorsal hippocampal SWRs, thalamo-cortical spindles, and cortical slow oscillations [143]. Notably,
307 the artificial enhancement of the coordination between dHPC ripples and down-state-spindle
308 complexes in the mPFC improves memory consolidation [144]. Thus, dHPC-cortical coordination is a
309 crucial mechanism for memory consolidation despite the limited anatomical connections between
310 the dHPC and mPFC [145,146]. The coordination between ventral ripples and cortical/thalamic slow
311 waves also increases after contextual fear learning, as well as ventral ripple events phase-locking to
312 cortical/thalamic spindles, albeit uncorrelated with memory performance at retrieval [147]. The
313 thalamic nucleus reuniens is emerging as a relay structure for the coordination between the ventral
314 and intermediate hippocampus and the mPFC [147,148]. To our knowledge, only one study has
315 established the functional implication of the monosynaptic connections from the ventral and
316 intermediate hippocampus to the mPFC during memory consolidation [149]. Systems consolidation
317 of emotional memories could thus involve direct or indirect coordination between the vHPC and
318 cortical areas, and/or triple coordination of dorsal and ventral hippocampus SWRs with cortical
319 oscillations.

320 **Concluding remarks and future perspectives**

321 The features of neurons along the dorso-ventral axis of the hippocampus display a gradient from
322 mostly spatial to mostly emotional, and the neural representations in the dHPC and vHPC are
323 involved in the expression of contextual and valenced memories through their connectivity with
324 other valence-related structures. Spatial memories are consolidated during sleep through neural
325 reactivation and the organization of neural activity by non-REM sleep SWRs and REM sleep theta
326 oscillations. Although these phenomena have been mostly studied in the dHPC, there are

327 preliminary indications that the same principles could hold for emotional memory consolidation in
328 the vHPC. However, most memories are complex and combine contextual and emotional
329 information. How is the contextual information transferred to structures that lack direct connectivity
330 with the dHPC? We propose that changes in the coordination between the dorsal and ventral
331 hippocampus through theta oscillations and SWRs might underlie the gating of contextual
332 information for their integration with valence information processed in the rest of the network,
333 including the BLA and mPFC. To directly test this hypothesis and more generally refine theories of
334 the processing of emotional information, the physiology of the vHPC and this area's connections
335 with the rest of the valence network deserve further investigation. For example, vHPC inputs to the
336 mPFC are anatomically and functionally segregated according to the depth of the projecting neurons
337 in the pyramidal layer: superficial neurons are preferentially connected to PFC inhibitory
338 interneurons and promote exploration, whereas deeper neuronal populations project to PFC
339 pyramidal neurons and fast-spiking interneurons, and promote avoidance [59]. In the dHPC, CA1
340 pyramidal neurons have different spatial properties depending on their depth [150,151], influencing
341 their recruitment into slow oscillations, SWRs, reactivation, and REM theta [146,152,153]. Can
342 similar gradients be found in the vHPC for spatial or valence-related properties? Crucially, it is still
343 unknown whether vHPC neuronal assemblies reactivate during vHPC ripples. If so, would the content
344 of the reactivation be exclusively valence-related or exhibit a mix of valence and contextual
345 information? Would vHPC reactivation be coordinated with contextual reactivation in the dHPC?
346 Overall, a better understanding of how ventral and dorsal hippocampal sleep SWRs and reactivation
347 differentially recruit other brain areas would help refine their respective roles during emotional
348 memory consolidation. Of note, a longstanding bias has restricted research on memory
349 consolidation to mostly males. While it is unclear how sex and hormonal variations affect spatial
350 memory, it is known that there are sex-dependent differences in fear conditioning [154] and that
351 hippocampal plasticity is susceptible to hormonal changes [155]. Because women are more
352 susceptible to PTSD and anxiety disorders, future research on emotional memory consolidation in
353 rodent models should strive to balance the sexes and carefully examine potential sex differences.
354 Finally, there is still a lack of both causal and physiological evidence supporting the involvement of
355 ventral theta oscillations during REM in memory consolidation. Overall, the vHPC holds significant
356 potential as a focal point for future research on emotional memory consolidation during sleep, with
357 particular attention to be paid to the pertinent anatomical connections between neural circuits.

358 **Box 1: Intrinsic and extrinsic hippocampal anatomical connectivity.** Anatomical studies have
359 revealed distinct connectivity patterns along the dorso-ventral axis of the rodent hippocampus and
360 the brain structures of the valence-processing network mentioned in this review. Unless specified,

361 these connections are glutamatergic. There are bidirectional connections all along the dorso-ventral
362 axis with the thalamic nucleus reuniens [156], thus considered the main relay between the
363 hippocampus and cortical areas. However, the medial prefrontal cortex receives direct input
364 from the intermediate and ventral hippocampus [53, 60], and has also marginal connections
365 with the dHPC [145,146].

366 . The NAc, part of the ventral striatum, receives inputs from all hippocampal subregions [131,133],
367 but no projections from the NAc to the hippocampus have been identified. The VTA is a
368 heterogeneous structure with intermingled dopaminergic, GABAergic, and a small population of
369 glutamatergic neurons. The VTA sends sparse dopaminergic innervation to the whole hippocampus
370 and glutamatergic projections to the dHPC which are thought to instruct the dHPC with reward
371 signals [157]. The VTA doesn't receive direct hippocampal inputs [158]. The BLA, a core structure of
372 the valence-processing network, has bidirectional connections with the ventral part of the
373 hippocampus only [138](Fig. 2B).

374 In this review, we hypothesize that the association of spatial information with valence information
375 might involve the transfer of spatial and emotional information along the dorso-ventral axis. These
376 could rely on at least two forms of intra-hippocampal anatomical connectivity. The first one is direct
377 long-range monosynaptic connections between the dorsal and ventral poles. Notably, dorsal CA2
378 neurons were shown to project to the ventral CA1 region implicated in social memory [159].
379 Additional long-range projections remain to be established. The second one is overlapping local
380 excitatory/inhibitory circuits along the dorsal-ventral axis that could synchronize through the
381 inhibitory interneurons and the recurrent collaterals of the CA3 pyramidal cells [76]. This indirect
382 path potentially underlies the coordination of SWRs and the traveling of theta waves. However, both
383 theta coherence and SWR coordination decrease drastically in the ventral pole [29,142], suggesting a
384 partial disconnection between the dorsal/intermediate and ventral hippocampus. Given the high
385 genomic, proteomics, cellular, and connectivity heterogeneity across the dorsal-ventral axis [5], and
386 the variation in the delineation of the hippocampal segments as a function of the chosen criteria, it
387 is difficult to identify the anatomical, cellular, and/or electrophysiological factors explaining this
388 coordination drop and the exact location of the ventral border. Because the excitability and GABA
389 release change along the dorso-ventral axis [160] and are modulated by learning, one may speculate
390 that environmental factors, such as learning from a highly emotional experience, may temporarily
391 modulate the excitability of dorsal and ventral neurons around the intermediate-ventral zone to
392 control for the coordination between the dorsal and ventral hippocampus (see Outstanding

393 questions). Alternatively, the dorsal and ventral poles could synchronize through the coordinating
394 influence of external structures.

395 **Acknowledgments**

396 We would like to thank the reviewers whose detailed comments contributed to substantially
397 improve this review. This work was supported by la Ville de Paris (GG, EP), The Fyssen Foundation,
398 The Schlumberger Foundation for Education and Research (FSER), Inserm (ATIP-Avenir), A BBRF
399 NARSAD Young Investigator Grant (G.G.), The Fyssen Foundation and EMBO ALTF 275-2021
400 postdoctoral fellowship (J.F.M.).

401

402 **Declaration of interests**

403 The authors declare no competing interest .

404

405 **References**

- 406 1. Krause, A.J. *et al.* (2017) The sleep-deprived human brain. *Nat. Rev. Neurosci.* 18, 404–418
- 407 2. Kensinger, E.A. and Ford, J.H. (2020) Retrieval of Emotional Events from Memory. *Annu. Rev.*
408 *Psychol.* 71, 251–272
- 409 3. Fanselow, M.S. and Dong, H.-W. (2010) Are the dorsal and ventral hippocampus functionally
410 distinct structures? *Neuron* 65, 7–19
- 411 4. Bannerman, D.M. *et al.* (2004) Regional dissociations within the hippocampus - Memory and
412 anxiety. *Neurosci. Biobehav. Rev.* 28, 273–283
- 413 5. Strange, B. A. *et al.* (2014) Functional organization of the hippocampal longitudinal axis. *Nat.*
414 *Rev. Neurosci.* 15, 655–669
- 415 6. Kjelstrup, K.G. *et al.* (2002) Reduced fear expression after lesions of the ventral hippocampus.
416 *Proc. Natl. Acad. Sci. U. S. A.* 99, 10825–30
- 417 7. Trivedi, M.A. and Coover, G.D. (2004) Lesions of the ventral hippocampus, but not the dorsal
418 hippocampus, impair conditioned fear expression and inhibitory avoidance on the elevated T-
419 maze. *Neurobiol. Learn. Mem.* 81, 172–184
- 420 8. Wang, M.E. *et al.* (2013) Differential roles of the dorsal and ventral hippocampus in predator
421 odor contextual fear conditioning. *Hippocampus* 000, n/a-n/a
- 422 9. Schumacher, A. *et al.* (2018) Ventral Hippocampal CA1 and CA3 Differentially Mediate Learned
423 Approach-Avoidance Conflict Processing. *Curr. Biol.* 28, 1318-1324.e4
- 424 10. O’Keefe, J. (1976) Place units in the hippocampus of the freely moving rat. *Exp. Neurol.* 51, 78–
425 109
- 426 11. Wilson, M.A. and McNaughton, B.L. (1993) Dynamics of the hippocampal ensemble code for
427 space. *Science* 261, 1055–8
- 428 12. Tolman, Edward C (1948) Cognitive maps in rats and men. *Psychol. Rev.* 55, 189–208
- 429 13. O’Keefe, J. and Nadel, L. (1978) *The hippocampus as a cognitive map*, Oxford University Press
- 430 14. Kubie, J.L. *et al.* (2020) Is hippocampal remapping the physiological basis for context?
431 *Hippocampus* 30, 851–864
- 432 15. Moita, M. a P. *et al.* (2004) Putting fear in its place: remapping of hippocampal place cells
433 during fear conditioning. *J. Neurosci. Off. J. Soc. Neurosci.* 24, 7015–23
- 434 16. Wang, M.E. *et al.* (2015) Extinction of Learned Fear Induces Hippocampal Place Cell
435 Remapping. *J. Neurosci.* 35, 9122–9136
- 436 17. Schuette, P.J. *et al.* (2020) Long-Term Characterization of Hippocampal Remapping during

- 437 Contextual Fear Acquisition and Extinction. *J. Neurosci.* 40, 8329–8342
- 438 18. Okada, S. *et al.* (2017) Spatial Representation of Hippocampal Place Cells in a T-Maze with an
439 Aversive Stimulation. 11
- 440 19. Hollup, S.A. *et al.* (2001) Accumulation of hippocampal place fields at the goal location in an
441 annular watermaze task. *J. Neurosci.* 21, 1635–1644
- 442 20. Gauthier, J.L. and Tank, D.W. (2018) A Dedicated Population for Reward Coding in the
443 Hippocampus. *Neuron* 99, 179-193.e7
- 444 21. Jung, M.W. *et al.* (1994) Comparison of Spatial Firing Characteristics of Units in Dorsal and
445 Ventral Hippocampus of the Rat. *J. Neurosci.* 14, 7347–7356
- 446 22. Kjelstrup, K.B. *et al.* (2008) Finite Scale of Spatial Representation in the Hippocampus. *Science*
447 321, 140–143
- 448 23. Keinath, A.T. *et al.* (2014) Precise spatial coding is preserved along the longitudinal
449 hippocampal axis. *Hippocampus* 24, 1533–1548
- 450 24. O’Keefe, J. and Recce, M.L. (1993) Phase relationship between hippocampal place units and the
451 EEG theta rhythm. *Hippocampus* 3, 317–30
- 452 25. Drieu, C. and Zugaro, M. (2019) Hippocampal Sequences During Exploration: Mechanisms and
453 Functions. *Front. Cell. Neurosci.* 13
- 454 26. Skaggs, W.E. *et al.* (1996) Theta phase precession in hippocampal neuronal populations and the
455 compression of temporal sequences. *Hippocampus* 6, 149–72
- 456 27. Royer, S. *et al.* (2010) Distinct representations and theta dynamics in dorsal and ventral
457 hippocampus. *J. Neurosci. Off. J. Soc. Neurosci.* 30, 1777–87
- 458 28. Kropff, E. *et al.* (2021) Frequency of theta rhythm is controlled by acceleration, but not speed,
459 in running rats. *Neuron* 109, 1029-1039.e8
- 460 29. Patel, J. *et al.* (2012) Traveling Theta Waves along the Entire Septotemporal Axis of the
461 Hippocampus. *Neuron* 75, 410–417
- 462 30. Chockanathan, U. and Padmanabhan, K. (2021) Divergence in Population Coding for Space
463 between Dorsal and Ventral CA1. *eNeuro* 8
- 464 31. Jin, S.-W. and Lee, I. (2021) Differential encoding of place value between the dorsal and
465 intermediate hippocampus. *Curr. Biol.* 31, 3053-3072.e5
- 466 32. Jarzebowski, P. *et al.* (2022) Different encoding of reward location in dorsal and intermediate
467 hippocampus. *Curr. Biol.* 32, 834-841.e5
- 468 33. Forro, T. *et al.* (2022) Anxiety-related activity of ventral hippocampal interneurons. *Prog.*
469 *Neurobiol.* 219, 102368
- 470 34. Jimenez, J.C. *et al.* (2018) Anxiety Cells in a Hippocampal-Hypothalamic Circuit. *Neuron* 97, 670-
471 683.e6
- 472 35. Ciochi, S. *et al.* (2015) Selective information routing by ventral hippocampal CA1 projection
473 neurons. *Science* 348, 560–563
- 474 36. Bagot, R.C. *et al.* (2015) Ventral hippocampal afferents to the nucleus accumbens regulate
475 susceptibility to depression. *Nat. Commun.* 6, 7062
- 476 37. Jimenez, J.C. *et al.* (2020) Contextual fear memory retrieval by correlated ensembles of ventral
477 CA1 neurons. *Nat. Commun.* 11, 3492
- 478 38. Herbst, M.R. *et al.* (2022) Ventral hippocampal shock encoding modulates the expression of
479 trace cued fear. *Neurobiol. Learn. Mem.* 190, 107610
- 480 39. Shpokayte, M. *et al.* (2022) Hippocampal cells segregate positive and negative engrams.
481 *Commun. Biol.* 5, 1–15
- 482 40. Biane, J.S. *et al.* (2023) Neural dynamics underlying associative learning in the dorsal and
483 ventral hippocampus. *Nat. Neurosci.* 26, 798–809
- 484 41. Yun, M. *et al.* (2023) Septotemporal variations in hippocampal value and outcome processing.
485 *Cell Rep.* 42, 112094
- 486 42. Nguyen, R. *et al.* (2023) Fear extinction relies on ventral hippocampal safety codes shaped by
487 the amygdala. *Sci. Adv.* 9, eadg4881

- 488 43. Robinson, N.T.M. *et al.* (2020) Targeted Activation of Hippocampal Place Cells Drives Memory-
489 Guided Spatial Behavior. *Cell* 183, 1586-1599.e10
- 490 44. Liu, X. *et al.* (2012) Optogenetic stimulation of a hippocampal engram activates fear memory
491 recall. *Nature* 484, 381–385
- 492 45. Ramirez, S. *et al.* (2013) Creating a false memory in the hippocampus. *Science* 341, 387–91
- 493 46. Redondo, R.L. *et al.* (2014) Bidirectional switch of the valence associated with a hippocampal
494 contextual memory engram. *Nature* 513, 426–430
- 495 47. Grella, S.L. *et al.* (2022) Reactivating hippocampal-mediated memories during reconsolidation
496 to disrupt fear. *Nat. Commun.* 13, 4733
- 497 48. Lacagnina, A.F. *et al.* (2019) Distinct hippocampal engrams control extinction and relapse of
498 fear memory. *Nat. Neurosci.* 22, 753–761
- 499 49. Chen, B.K. *et al.* (2019) Artificially Enhancing and Suppressing Hippocampus-Mediated
500 Memories. *Curr. Biol.* 29, 1885-1894.e4
- 501 50. Graham, J. *et al.* (2021) High-Frequency Stimulation of Ventral CA1 Neurons Reduces Amygdala
502 Activity and Inhibits Fear. *Front. Behav. Neurosci.* 15
- 503 51. Ortiz, S. *et al.* (2019) Anterior Cingulate Cortex and Ventral Hippocampal Inputs to the
504 Basolateral Amygdala Selectively Control Generalized Fear. *J. Neurosci.* 39, 6526–6539
- 505 52. Padilla-Coreano, N. *et al.* (2016) Direct Ventral Hippocampal-Prefrontal Input Is Required for
506 Anxiety-Related Neural Activity and Behavior. *Neuron* 89, 857–866
- 507 53. Kim, W.B. and Cho, J.H. (2017) Encoding of Discriminative Fear Memory by Input-Specific LTP in
508 the Amygdala. *Neuron* 95, 1129-1146.e5
- 509 54. Xu, C. *et al.* (2016) Distinct Hippocampal Pathways Mediate Dissociable Roles of Context in
510 Memory Retrieval. *Cell* DOI: 10.1016/j.cell.2016.09.051
- 511 55. Zhou, Y. *et al.* (2019) A ventral CA1 to nucleus accumbens core engram circuit mediates
512 conditioned place preference for cocaine. *Nat. Neurosci.* 22, 1986–1999
- 513 56. Szadzinska, W. *et al.* (2021) Hippocampal Inputs in the Prelimbic Cortex Curb Fear after
514 Extinction. *J. Neurosci.* 41, 9129–9140
- 515 57. Marek, R. *et al.* (2018) Hippocampus-driven feed-forward inhibition of the prefrontal cortex
516 mediates relapse of extinguished fear. *Nat. Neurosci.* 21, 384–392
- 517 58. Twining, R.C. *et al.* (2020) Ventral Hippocampal Input to the Prelimbic Cortex Dissociates the
518 Context from the Cue Association in Trace Fear Memory. *J. Neurosci.* 40, 3217–3230
- 519 59. Sánchez-Bellot, C. *et al.* (2022) Two opposing hippocampus to prefrontal cortex pathways for
520 the control of approach and avoidance behaviour. *Nat. Commun.* 13, 339
- 521 60. Yeates, D.C.M. *et al.* (2022) Parallel ventral hippocampus-lateral septum pathways
522 differentially regulate approach-avoidance conflict. *Nat. Commun.* 13, 3349
- 523 61. Felix-Ortiz, A.C. *et al.* (2013) BLA to vHPC Inputs Modulate Anxiety-Related Behaviors. *Neuron*
524 79, 658–664
- 525 62. Pi, G. *et al.* (2020) Posterior basolateral amygdala to ventral hippocampal CA1 drives approach
526 behaviour to exert an anxiolytic effect. *Nat. Commun.* 11, 183
- 527 63. Ma, H. *et al.* (2021) Amygdala-hippocampal innervation modulates stress-induced depressive-
528 like behaviors through AMPA receptors. *Proc. Natl. Acad. Sci.* 118, e2019409118
- 529 64. Huff, M.L. *et al.* (2016) Basolateral amygdala projections to ventral hippocampus modulate the
530 consolidation of footshock, but not contextual, learning in rats. *Learn. Mem.* 23, 51–60
- 531 65. Wang, G.-W. *et al.* (2017) Post-training reversible disconnection of the ventral hippocampal–
532 basolateral amygdaloid circuits impairs consolidation of inhibitory avoidance memory in rats.
533 *Learn. Mem.* 24, 602–606
- 534 66. Beyeler, A. *et al.* (2016) Divergent Routing of Positive and Negative Information from the
535 Amygdala during Memory Retrieval. DOI: 10.1016/j.neuron.2016.03.004
- 536 67. Bian, X.-L. *et al.* (2019) Anterior Cingulate Cortex to Ventral Hippocampus Circuit Mediates
537 Contextual Fear Generalization. *J. Neurosci.* 39, 5728–5739
- 538 68. Cullen, P.K. *et al.* (2015) Activity of the anterior cingulate cortex and ventral hippocampus

- 539 underlie increases in contextual fear generalization. *Neurobiol. Learn. Mem.* 124, 19–27
- 540 69. Pavlides, C. and Winson, J. (1989) Influences of hippocampal place cell firing in the awake state
541 on the activity of these cells during subsequent sleep episodes. *J. Neurosci. Off. J. Soc.*
542 *Neurosci.* 9, 2907–18
- 543 70. Wilson, M.A. and McNaughton, B.L. (1994) Reactivation of Hippocampal Ensemble Memories
544 During Sleep. *Science* 265, 676–679
- 545 71. Skaggs, W.E. and McNaughton, B.L. (1996) Replay of neuronal firing sequences in rat
546 hippocampus during sleep following spatial experience. *Science* 271, 1870–3
- 547 72. Lee, A.K. and Wilson, M.A. (2002) Memory of Sequential Experience in the Hippocampus
548 during Slow Wave Sleep. *Neuron* 36, 1183–1194
- 549 73. Pfeiffer, B.E. (2018) The content of hippocampal “replay.” *Hippocampus* DOI:
550 10.1002/hipo.22824
- 551 74. Chen, Z.S. and Wilson, M.A. (2023) How our understanding of memory replay evolves. *J.*
552 *Neurophysiol.* 129, 552–580
- 553 75. Genzel, L. *et al.* (2020) A consensus statement: defining terms for reactivation analysis. *Philos.*
554 *Trans. R. Soc. B Biol. Sci.* 375, 20200001
- 555 76. Buzsáki, G. (2015) Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory
556 and planning. *Hippocampus* 25, 1073–1188
- 557 77. Norimoto, H. *et al.* (2018) Hippocampal ripples down-regulate synapses. *Science* 1527, 1–8
- 558 78. Sadowski, J.H.L.P. *et al.* (2016) Sharp-Wave Ripples Orchestrate the Induction of Synaptic
559 Plasticity during Reactivation of Place Cell Firing Patterns in the Hippocampus. *Cell Rep.* 14,
560 1916–1929
- 561 79. Zhou, Z. and Norimoto, H. (2023) Sleep sharp wave ripple and its functions in memory and
562 synaptic plasticity. *Neurosci. Res.* 189, 20–28
- 563 80. Girardeau, G. *et al.* (2009) Selective suppression of hippocampal ripples impairs spatial
564 memory. *Nat. Neurosci.* 12, 1222–3
- 565 81. Ego-Stengel, V. and Wilson, M.A. (2009) Disruption of ripple-associated hippocampal activity
566 during rest impairs spatial learning in the rat. *Hippocampus* DOI: 10.1002/hipo.20707
- 567 82. Wang, D.V. *et al.* (2015) Mesopontine median raphe regulates hippocampal ripple oscillation
568 and memory consolidation. *Nat. Neurosci.* 18
- 569 83. Gridchyn, I. *et al.* (2020) Assembly-Specific Disruption of Hippocampal Replay Leads to
570 Selective Memory Deficit. *Neuron* 106, 291-300.e6
- 571 84. McNamara, C.G. *et al.* (2014) Dopaminergic neurons promote hippocampal reactivation and
572 spatial memory persistence. *Nat. Neurosci.* 17, 1658–60
- 573 85. Laventure, S. and Benchenane, K. (2019) Validating the theoretical bases of sleep reactivation
574 during sharp-wave ripples and their association with emotional valence. DOI:
575 10.1002/hipo.23143
- 576 86. De Lavilleon, G. *et al.* (2013) Explicit memory creation during sleep: a causal role of place cell
577 on navigation. DOI: 10.1038/nn.3970
- 578 87. Bergado, J.A. *et al.* (2011) Emotional tagging—A simple hypothesis in a complex reality. *Prog.*
579 *Neurobiol.* 94, 64–76
- 580 88. Michon, F. *et al.* (2019) Post-learning Hippocampal Replay Selectively Reinforces Spatial
581 Memory for Highly Rewarded Locations. *Curr. Biol.* 29, 1436-1444.e5
- 582 89. Lammel, S. *et al.* (2012) Input-specific control of reward and aversion in the ventral tegmental
583 area. *Nature* 491, 212–217
- 584 90. Tsetsenis, T. *et al.* (2023) Dopaminergic regulation of hippocampal plasticity, learning, and
585 memory. *Front. Behav. Neurosci.* 16
- 586 91. Foster, D.J. and Wilson, M. a (2006) Reverse replay of behavioural sequences in hippocampal
587 place cells during the awake state. *Nature* 440, 680–3
- 588 92. Atherton, L.A. *et al.* (2015) Memory trace replay : the shaping of memory consolidation by
589 neuromodulation. *Trends Neurosci.* DOI: 10.1016/j.tins.2015.07.004

- 590 93. Singer, A.C. and Frank, L.M. (2009) Rewarded outcomes enhance reactivation of experience in
591 the hippocampus. *Neuron* 64, 910–21
- 592 94. Ambrose, R.E. *et al.* (2016) Reverse Replay of Hippocampal Place Cells Is Uniquely Modulated
593 by Changing Reward. *Neuron* 91, 1–13
- 594 95. Pfeiffer, B.E. and Foster, D.J. (2013) Hippocampal place-cell sequences depict future paths to
595 remembered goals. *Nature* DOI: 10.1038/nature12112
- 596 96. Carey, A.A. *et al.* (2019) Reward revaluation biases hippocampal replay content away from the
597 preferred outcome. *Nat. Neurosci.* 22, 1450–1459
- 598 97. Wu, C. *et al.* (2017) Hippocampal awake replay in fear memory retrieval. *Nat. Neurosci.* DOI:
599 10.1038/nn.4507
- 600 98. Ormond, J. *et al.* (2023) Enhanced reactivation of remapping place cells during aversive
601 learning. *J. Neurosci.* DOI: 10.1523/JNEUROSCI.1450-22.2022
- 602 99. Tomar, A. *et al.* (2021) Stress enhances hippocampal neuronal synchrony and alters ripple-
603 spike interaction. *Neurobiol. Stress* 14, 100327
- 604 100. Tomar, A. and McHugh, T.J. (2022) The impact of stress on the hippocampal spatial code.
605 *Trends Neurosci.* 45, 120–132
- 606 101. Phillips, R.G. and LeDoux, J.E. (1992) Differential contribution of amygdala and hippocampus to
607 cued and contextual fear conditioning. *Behav. Neurosci.* 106, 274–85
- 608 102. Tovote, P. *et al.* (2015) Neuronal circuits for fear and anxiety. *Nat. Rev. Neurosci.* 16, 317–331
- 609 103. Giustino, T.F. and Maren, S. (2015) The Role of the Medial Prefrontal Cortex in the Conditioning
610 and Extinction of Fear. *Front. Behav. Neurosci.* 9
- 611 104. Terranova, J.I. *et al.* (2022) Hippocampal-amygdala memory circuits govern experience-
612 dependent observational fear. *Neuron* 110, 1–16
- 613 105. Hölscher, C. *et al.* (1997) Stimulation on the Positive Phase of Hippocampal Theta Rhythm
614 Induces Long-Term Potentiation That Can Be Depotentiated by Stimulation on the Negative
615 Phase in Area CA1 In Vivo. *J. Neurosci.* 17, 6470–6477
- 616 106. Hyman, J.M. *et al.* (2003) Stimulation in Hippocampal Region CA1 in Behaving Rats Yields Long-
617 Term Potentiation when Delivered to the Peak of Theta and Long-Term Depression when
618 Delivered to the Trough. *J. Neurosci.* 23, 11725–11731
- 619 107. Nuñez, A. and Buño, W. (2021) The Theta Rhythm of the Hippocampus: From Neuronal and
620 Circuit Mechanisms to Behavior. *Front. Cell. Neurosci.* 15
- 621 108. Seidenbecher, T. *et al.* (2003) Amygdalar and hippocampal theta rhythm synchronization
622 during fear memory retrieval. *Science* 301, 846–50
- 623 109. Narayanan, R.T. *et al.* (2007) Dissociated theta phase synchronization in amygdalo-
624 hippocampal circuits during various stages of fear memory. *Eur. J. Neurosci.* 25, 1823–31
- 625 110. Lesting, J. *et al.* (2013) Directional theta coherence in prefrontal cortical to amygdalo-
626 hippocampal pathways signals fear extinction. *PLoS One* 8, e77707
- 627 111. Likhtik, E. *et al.* (2013) Prefrontal entrainment of amygdala activity signals safety in learned
628 fear and innate anxiety. *Nat. Neurosci.* DOI: 10.1038/nn.3582
- 629 112. Dejean, C. *et al.* (2016) Prefrontal neuronal assemblies temporally control fear behaviour.
630 *Nature* 535, 420–424
- 631 113. Karalis, N. *et al.* (2016) 4-Hz oscillations synchronize prefrontal–amygdala circuits during fear
632 behavior. *Nat. Neurosci.* DOI: 10.1038/nn.4251
- 633 114. Mikulovic, S. *et al.* (2018) Ventral hippocampal OLM cells control type 2 theta oscillations and
634 response to predator odor. *Nat. Commun.* 9, 3638
- 635 115. Adhikari, A. *et al.* (2010) Synchronized Activity between the Ventral Hippocampus and the
636 Medial Prefrontal Cortex during Anxiety. *Neuron* 65, 257–269
- 637 116. Adhikari, A. *et al.* (2011) Single units in the medial prefrontal cortex with anxiety-related firing
638 patterns are preferentially influenced by ventral hippocampal activity. *Neuron* 71, 898–910
- 639 117. Padilla-Coreano, N. *et al.* (2019) Hippocampal-Prefrontal Theta Transmission Regulates
640 Avoidance Behavior. *Neuron* 104

- 641 118. Ackermann, S. and Rasch, B. (2014) Differential Effects of Non-REM and REM Sleep on Memory
642 Consolidation? *Curr. Neurol. Neurosci. Rep.* 14, 430
- 643 119. Lehmann, M. *et al.* (2016) Emotional arousal modulates oscillatory correlates of targeted
644 memory reactivation during NREM, but not REM sleep. *Sci. Rep.* 6, 39229
- 645 120. Boyce, R. *et al.* (2016) Causal evidence for the role of REM sleep theta rhythm in contextual
646 memory consolidation. *Science* 23, 812
- 647 121. Ravassard, P. *et al.* (2016) REM Sleep-Dependent Bidirectional Regulation of Hippocampal-
648 Based Emotional Memory and LTP. *Cereb. Cortex* 26, 1488–1500
- 649 122. Kudrimoti, H.S. *et al.* (1999) Reactivation of Hippocampal Cell Assemblies: Effects of Behavioral
650 State, Experience, and EEG Dynamics. *J. Neurosci.* 19, 4090–4101
- 651 123. Louie, K. and Wilson, M.A. (2001) Temporally Structured Replay of Awake Hippocampal
652 Ensemble Activity during Rapid Eye Movement Sleep. *Neuron* 29, 145–156
- 653 124. Zielinski, M.C. *et al.* (2021) Hippocampal theta sequences in REM sleep during spatial
654 learning [bioRxiv, 2021.04.15.439854](https://doi.org/10.1101/2021.04.15.439854)
- 655 125. Grosmark, A.D. *et al.* (2012) REM Sleep Reorganizes Hippocampal Excitability. *Neuron* 75,
656 1001–1007
- 657 126. Popa, D. *et al.* (2010) Coherent amygdalocortical theta promotes fear memory consolidation
658 during paradoxical sleep. *Proc. Natl. Acad. Sci. U. S. A.* 107, 6516–6519
- 659 127. Totty, M.S. *et al.* (2017) Sleep-Dependent Oscillatory Synchronization: A Role in Fear Memory
660 Consolidation. *Front. Neural Circuits* 11, 49
- 661 128. Girardeau, G. *et al.* (2017) Reactivations of emotional memory in the hippocampus-amygdala
662 system during sleep. *Nat. Neurosci.* 20
- 663 129. Lubenov, E.V. and Siapas, A.G. (2009) Hippocampal theta oscillations are travelling waves.
664 *Nature* 459, 534–9
- 665 130. Han, Y. *et al.* (2016) Enhanced theta synchronization correlates with the successful retrieval of
666 trace fear memory. *Biochem. Biophys. Res. Commun.* 480, 608–614
- 667 131. Sosa, M. *et al.* (2020) Dorsal and Ventral Hippocampal Sharp-Wave Ripples Activate Distinct
668 Nucleus Accumbens Networks. *Neuron* 105, 725-741.e8
- 669 132. Sjulson, L. *et al.* (2018) Cocaine Place Conditioning Strengthens Location-Specific Hippocampal
670 Coupling to the Nucleus Accumbens. *Neuron* 98, 926-934.e5
- 671 133. Trouche, S. *et al.* (2019) A Hippocampus-Accumbens Tripartite Neuronal Motif Guides
672 Appetitive Memory in Space. *Cell* 176, 1393-1406.e16
- 673 134. Gomperts, S.N. *et al.* (2015) VTA neurons coordinate with the hippocampal reactivation of
674 spatial experience. *eLife* 4, 321–352
- 675 135. Pennartz, C.M. *a et al.* (2004) The ventral striatum in off-line processing: ensemble reactivation
676 during sleep and modulation by hippocampal ripples. *J. Neurosci. Off. J. Soc. Neurosci.* 24,
677 6446–56
- 678 136. Lansink, C.S. *et al.* (2009) Hippocampus leads ventral striatum in replay of place-reward
679 information. *PLoS Biol.* 7, e1000173
- 680 137. van der Meer, M. a a and Redish, a D. (2011) Theta phase precession in rat ventral striatum
681 links place and reward information. *J. Neurosci. Off. J. Soc. Neurosci.* 31, 2843–54
- 682 138. Pitkänen, A. *et al.* (2000) Reciprocal Connections between the Amygdala and the Hippocampal
683 Formation, Perirhinal Cortex, and Postrhinal Cortex in Rat: A Review. *Ann. N. Y. Acad. Sci.* 911,
684 369–391
- 685 139. Tao, S. *et al.* (2021) Whole-Brain Mapping the Direct Inputs of Dorsal and Ventral CA1
686 Projection Neurons. *Front. Neural Circuits* 15
- 687 140. Zhu, H. *et al.* (2014) Chemogenetic Inactivation of Ventral Hippocampal Glutamatergic Neurons
688 Disrupts Consolidation of Contextual Fear Memory. *Neuropsychopharmacology* 39, 1880–1892
- 689 141. Miyawaki, H. and Mizuseki, K. (2022) De novo inter-regional coactivations of preconfigured
690 local ensembles support memory. *Nat. Commun.* 13, 1272
- 691 142. Patel, J. *et al.* (2013) Local generation and propagation of ripples along the septotemporal axis

692 of the hippocampus. *J Neurosci* 33, 17029–17041

693 143. Girardeau, G. and Lopes-dos-Santos, V. (2021) Brain neural patterns and the memory function
694 of sleep. *Science* 374, 560–564

695 144. Maingret, N. *et al.* (2016) Hippocampo-cortical coupling mediates memory consolidation
696 during sleep. *Nat Neurosci* 19, 959–964

697 145. Malik, R. *et al.* (2022) Top-down control of hippocampal signal-to-noise by prefrontal long-
698 range inhibition. *Cell* 185, 1602-1617.e17

699 146. Harvey, R.E. *et al.* (2023) Hippocampo-cortical circuits for selective memory encoding, routing,
700 and replay. *Neuron* 111, 2076-2090.e9

701 147. Bozic, I. *et al.* (2023) Coupling between the prelimbic cortex, nucleus reuniens, and
702 hippocampus during NREM sleep remains stable under cognitive and homeostatic demands.
703 *Eur. J. Neurosci.* 57, 106–128

704 148. Angulo-Garcia, D. *et al.* (2020) Cell Assemblies in the Cortico-Hippocampal-Reuniens Network
705 during Slow Oscillations. *J. Neurosci.* 40, 8343–8354

706 149. Binder, S. *et al.* (2019) Monosynaptic Hippocampal-Prefrontal Projections Contribute to Spatial
707 Memory Consolidation in Mice. *J. Neurosci.* 39, 6978–6991

708 150. Geiller, T. *et al.* (2017) Place cells are more strongly tied to landmarks in deep than in
709 superficial CA1. *Nat. Commun.* 8, 14531

710 151. Danielson, N.B. *et al.* (2016) Sublayer-Specific Coding Dynamics during Spatial Navigation and
711 Learning in Hippocampal Area CA1. *Neuron* 91, 652–665

712 152. Valero, M. *et al.* (2015) Determinants of different deep and superficial CA1 pyramidal cell
713 dynamics during sharp-wave ripples. *Nat. Neurosci.* 18, 1281–1290

714 153. Mizuseki, K. *et al.* (2011) Hippocampal CA1 pyramidal cells form functionally distinct sublayers.
715 *Nat. Neurosci.* 14, 1174–1181

716 154. Bauer, E.P. (2023) Sex differences in fear responses: Neural circuits. *Neuropharmacology* 222,
717 109298

718 155. Rocks, D. and Kundakovic, M. (2023) Hippocampus-based behavioral, structural, and molecular
719 dynamics across the estrous cycle. *J. Neuroendocrinol.* 35, e13216

720 156. Varela, C. *et al.* (2014) Anatomical substrates for direct interactions between hippocampus,
721 medial prefrontal cortex, and the thalamic nucleus reuniens. *Brain Struct. Funct.* 219, 911–929

722 157. Han, Y. *et al.* (2020) Excitatory VTA to DH projections provide a valence signal to memory
723 circuits. *Nat. Commun.* 11, 1466

724 158. Lisman, J.E. and Grace, A. a (2005) The hippocampal-VTA loop: controlling the entry of
725 information into long-term memory. *Neuron* 46, 703–13

726 159. Meira, T. *et al.* (2018) A hippocampal circuit linking dorsal CA2 to ventral CA1 critical for social
727 memory dynamics. *Nat. Commun.* 9, 1–14

728 160. Milior, G. *et al.* (2016) Electrophysiological Properties of CA1 Pyramidal Neurons along the
729 Longitudinal Axis of the Mouse Hippocampus. *Sci. Rep.* 6, 38242

730

731

732

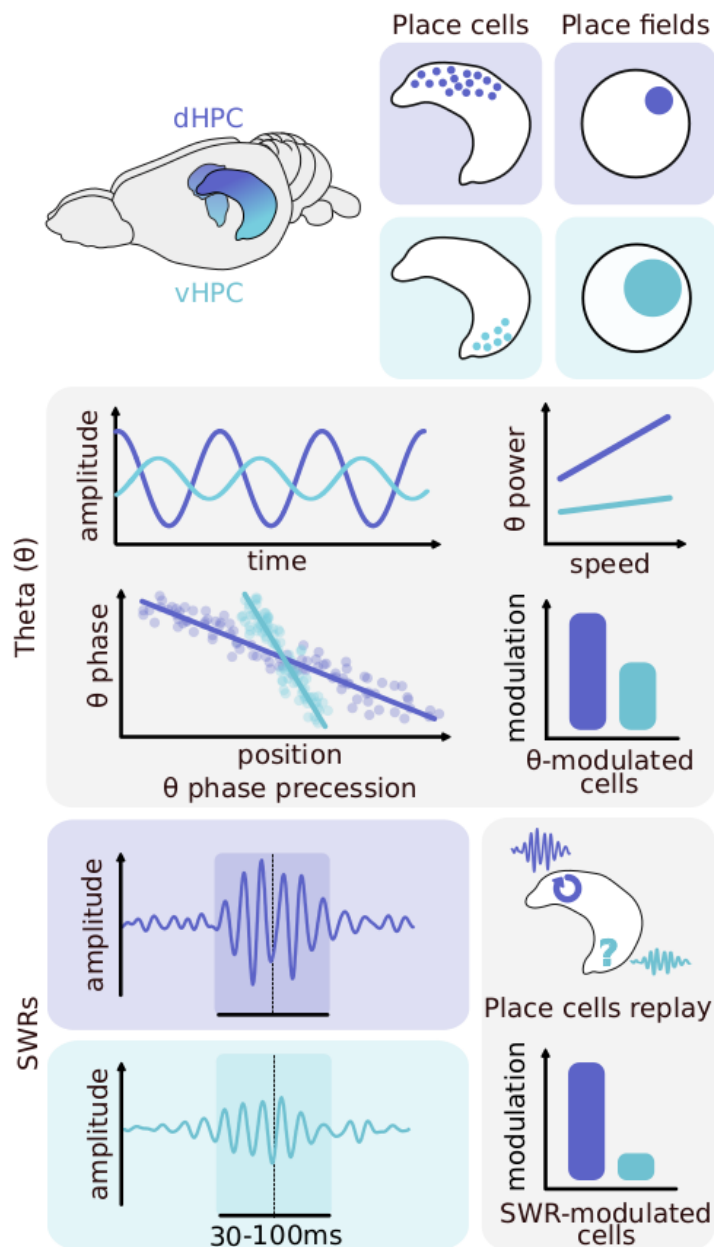
733

734

735

736

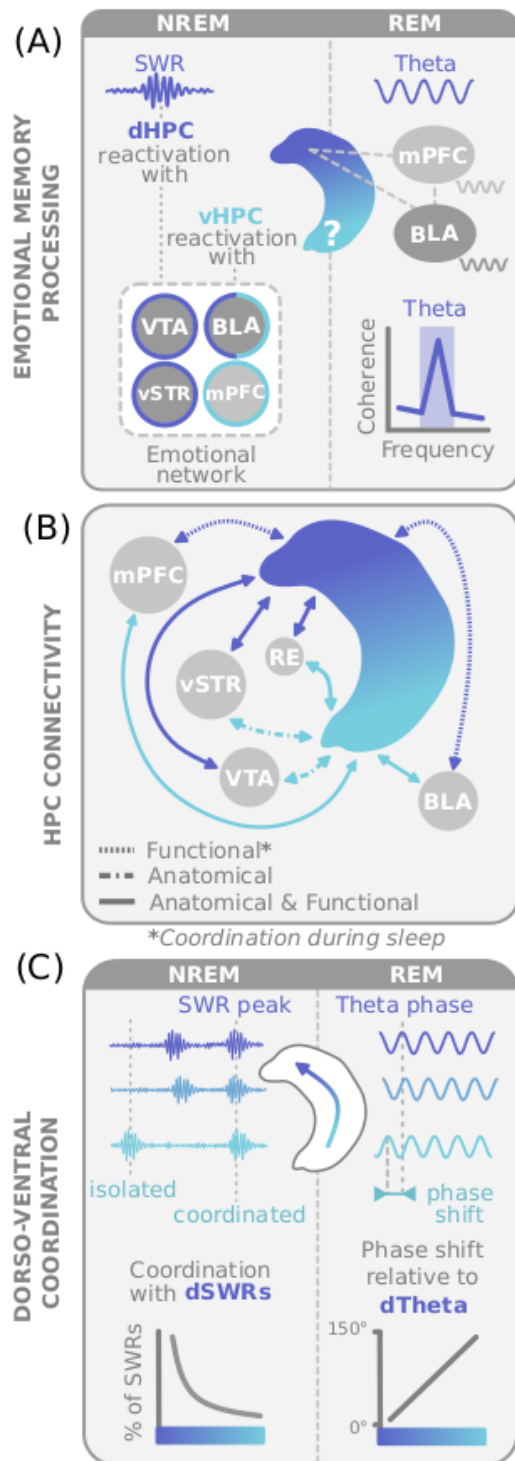
737



738

739

Figure 1. Firing properties of rodent hippocampal neurons along the dorso-ventral axis. Compared
 740 to the dHPC, vHPC place cells are fewer and have larger place fields [21,22]. Phase precession, the
 741 process by which place cell activity occurs at earlier phases of theta (θ) as the animal crosses the
 742 place field, is slower in the vHPC [22]. During navigation, θ power is lower in the vHPC than in the
 743 dHPC, and vHPC cells are less θ -modulated than dorsal ones: their firing is more dispersed across
 744 different θ phases [27]. θ power correlates with speed in dHPC but not vHPC [29]. Ripple amplitude
 745 is lower in vHPC than in the dHPC, and vHPC cells are less ripple-modulated than dHPC ones [142]. It
 746 is yet unknown whether the reactivation described in the dHPC also occurs in the vHPC.



747

748

749 **Figure 2. Anatomical-functional characteristics throughout the hippocampus during sleep.** A. The
 750 hippocampus is involved in emotional processing during sleep. During NREM or quiet wakefulness,
 751 and preferentially during ripples (SWR), following reward/aversive learning, there are coordinated
 752 reactivations between the dHPC and valence-processing structures: ventral striatum (vSTR), ventral
 753 tegmental area (VTA), and basolateral amygdala (BLA);[128,135,136]. The vHPC was shown to

754 reactivate with the BLA and the medial prefrontal cortex (mPFC)[141]. During REM sleep following
755 aversive learning, theta coherence increases between dHPC, BLA, and the medial prefrontal cortex
756 (mPFC)[126] **B.** The observations summarized in (A) can only be partially explained by the anatomo-
757 functional connectivity of the hippocampus along the dorso-ventral axis. Functional connections
758 indicate that oscillatory or neuronal coordination between the hippocampus and the other
759 structures represented in the graph have been described during sleep and correlated with memory
760 formation. **C.** Oscillations propagating along the hippocampal dorso-ventral axis during sleep could
761 mediate the transfer of contextual and emotional information along the longitudinal axis and
762 towards the other structures of the emotional network. During NREM, dorso-ventral SWRs
763 coordination decreases along the axis, and most vHPC SWRs are isolated from dorsal ones. During
764 REM, theta oscillations travel across the dorso-ventral axis and their phase shifts [29,142].

Highlights

- The rodent dorsal hippocampus displays spatial representations that can be biased by the positive or negative valence of the environment.
- The ventral hippocampus displays poorer spatial coding properties than dHPC but stronger valence-related processing.
- The reactivation of spatial representations in the dHPC that sustain spatial memory consolidation can occur conjointly with valence-processing structures despite limited direct anatomical connections.
- The vHPC has reciprocal connections with key structures of the valence-processing network such as the basolateral amygdala or medial prefrontal cortex.
- The vHPC has the potential to serve as a central hub for the integration of contextual information from the dorsal hippocampus and valence information from the rest of the network during sleep-dependent consolidation, through theta oscillations during REM sleep and sharp-wave ripples during Non-REM sleep.

Outstanding questions

- It is now firmly established that dHPC ripples and the associated neural reactivation are necessary for spatial memory consolidation. Surprisingly, it is still unknown whether there is neural reactivation in the vHPC during sleep. If so, would vHPC reactivation also be associated with vHPC ripples? Would vHPC reactivation also sustain memory consolidation, and if so, which type of memory? We would expect vHPC ripples and reactivation to be more specifically involved in the consolidation of emotionally charged memories. A better characterization of ripple parameters and ripple-associated neural activity during consolidation in the vHPC is required.
- Ripples and theta oscillations are weakly coordinated along the dorso-ventral axis in the absence of consolidation requirements (i.e. previous learning or exploration). How is the dorso-ventral coordination during sleep affected by the valence of the preceding experience? What are the anatomical underpinnings of disconnection vs. coordination? Is the mechanism intra-hippocampal, or does it involve third-party coordinating structures?
- The physiological underpinnings of the role of REM sleep for emotional memory consolidation are still unclear. Could REM sleep be more important for vHPC-mediated emotional processing, as opposed to NREM for dHPC-mediated spatial processing?
- How does emotional valence during encoding influence sleep reactivation in the dorsal hippocampus? What are the mechanisms underlying these processes, and do they involve other structures like the BLA, known to mediate the potentiating effects of stress on memory formation?