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Review

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

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

Highlights

The rodent dorsal hippocampus (dHPC) displays spatial representations that can be biased by the positive or negative valence of the environment.

The ventral hippocampus (vHPC) displays poorer spatial coding properties than the 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 dHPC and valence information from the rest of the network during sleep-dependent consolidation, through theta oscillations during rapid eye movement (REM) sleep and sharp-wave ripples during Non-REM sleep.

The hippocampus and spatial and emotional memory consolidation during sleep

Sleep is a physiological state present throughout the entire animal kingdom. In mammals, a characteristic feature of sleep is a reversible loss of consciousness associated with behavioral quiescence. This vulnerable state plays a vital role in the proper functioning of various organs, particularly the brain. Sleep deprivation notably impairs two interconnected cognitive processes: memory consolidation; that is, the gradual strengthening of memories over time, and emotional processing [1]. Emotions have the potential to enhance memory formation, as experiences that evoke positive or negative emotional responses are more effectively remembered [2]. Specific contexts can also be associated with emotions, forming direct associations so that the emotion is re-experienced when exposed to the same context, a phenomenon modeled in rodents with contextual fear conditioning (CFC). Emotions are characterized by their valence, which can range from negative to positive, and by their intensity, which will in turn influence the arousal level triggered by the emotion. Both valence and intensity influence the processing of the emotion and its effect on memory. Extensive research in rodents has focused on studying how the physiology of the dHPC, a central structure for contextual memory, contributes to the encoding, consolidation, and retrieval of spatial memories during both wakefulness and sleep. The vHPC is considered functionally distinct from the dHPC, and a large body of selective lesions and pharmacological inactivation studies established its role in emotional processing, especially stress-, fear-, and anxiety-related behaviors [3–9]. Here, we review the rodent literature to first compare the known spatial and emotional features of the dHPC and vHPC. We then discuss evidence supporting the notion that the interactions between the hippocampus and other core valence-processing structures, such as the basolateral amygdala (BLA), nucleus accumbens (NAc),

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anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC), are crucial for the processing of spatial and emotional information during sleep. We argue for a potential role of the vHPC as a central hub for integrating context and valence information, contributing to emotional memory acquisition and retrieval, as well as consolidation during sleep. Investigating well-known mechanisms of dHPC-like neural reactivation, NREM sleep sharp-wave ripples, and REM sleep theta oscillation in the vHPC in the context of emotional memory consolidation and exploring how the valence of an experience modulates dorsoventral coordination during sleep will deepen current understanding of how contextual information is processed in parallel or convergence across the hippocampus dorsoventral axis and associated with emotional information to consolidate the memory of emotional experiences.

Spatial and emotional neural representations along the hippocampus dorsoventral axis

The hippocampus contains place cells that selectively activate at particular locations of an environment, called the place field [10,11]. Hippocampal place cells form cognitive maps [12,13] believed to sustain spatial learning. The exposure to a completely different environment can lead to drastic reconfiguration of the hippocampal cognitive map, a process referred to as global remapping, but more moderate changes in the environment, like spatial stretching, reshaping, and adding or removing sensory cues lead to more subtle changes in the spatial representation: in some cases, place cells only change their firing rate (referred to as rate remapping), and in other cases a subset of cells changes the location of their place-fields (referred to as partial remapping) [14]. In the dHPC, spatial representations can be modulated by the emotional valence of an experience. For instance, the introduction or removal of an aversive footshock in an environment, such as in CFC and extinction, respectively, triggers remapping [15–17]. Place fields tend to relocate towards locations associated with positive valence (or reward), referred to as goal-directed remapping, or towards locations associated with negative valence (e.g., due to an air puff), leading to a higher density of place fields around emotionally salient zones [18,19]. A subset of dHPC cells activates specifically at reward sites, independently of their location, thus directly encoding positive valence independently of space (reward cells) [20]. In addition, there are dHPC cells specifically active during freezing, a typical fear-related behavior [17]. Representations in the dHPC are therefore mostly spatial but can adapt to integrate valence-related information.

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

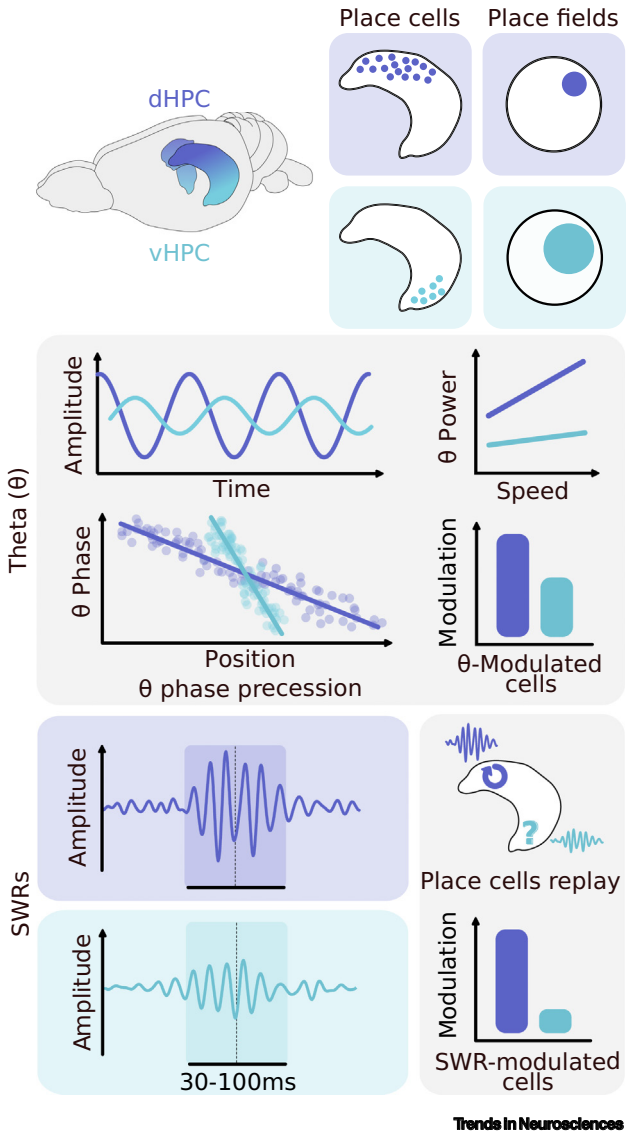

Figure 1. Firing properties of rodent hippocampal neurons along the dorsoventral axis. Compared with the dHPC, vHPC place cells are fewer and have larger place fields [21,22]. Phase precession, the process by which place cell activity occurs at earlier phases of theta (θ) as the animal crosses the place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

responsive cells in the vHPC [37,38], and different subpopulations respond to aversive stimuli versus reward [39].

In ethological contexts, it is crucial to associate specific places with salient emotional experiences, to find food or stay hypervigilant in a zone where a predator was previously encountered. It is therefore difficult to disambiguate spatial and emotional learning. The vast majority of studies on spatial coding and memory use rewards to stimulate exploration, making them inherently positively valenced. Still, it is possible to design experiments to reveal nonspatial emotional properties of the hippocampus. For example, two recent studies in head-fixed animals using odors associated with reward or punishment found that the vHPC was more responsive to the predicted positive or negative outcome of the odor [40,41]. vHPC neurons also respond to the sound stimulus predicting the shock during cued fear extinction [42]. Thus, both the dorsal and vHPC display a mix of valence-related and spatial features, but the representations are heavily biased towards space in the dHPC and towards valence and salience in the vHPC, sustaining the functional gradient from spatial to emotional along the dorsoventral axis.

Hippocampal representations support the retrieval of emotional memories

The term engram has been often used to indicate the population of neurons that constitute the physical trace of a memory in the brain and whose activation supports the retrieval of this memory. Can hippocampal space and valence representations be seen as engrams for emotional memories? In other words, can the activation of dHPC or vHPC representations trigger emotion-related behaviors, effectively constituting the support of emotional memory recall? A series of studies leveraged tagging and optogenetics methods to address this question. In the dHPC, optogenetic activation of neuronal ensembles previously associated with a positive (reward) or negative (footshock) environment is sufficient to trigger the behavior related to the emotional experience (e.g., licking for reward or freezing) in another, neutral environment [43,44]. These associations between the valence and the spatial representation can also be artificially manipulated: for example, when the optoactivation of a neutral spatial representation is paired with a footshock, the activation of this initially neutral representation subsequently triggers freezing in a neutral environment [45]. The associations between hippocampal neurons representing a specific context and an emotional valence, can also be reversed from positive to negative, and a freezing response in a negatively valenced environment can be reduced by the optoactivation of a competitive engram associated with a positive valence [46,47]. Finally, extinction training; that is, re-exposing an animal to a conditioned stimulus without any threat, suppresses the activation of a dHPC fear engram while activating a new extinction engram: manipulating those distinct engrams directly impacts extinction and relapse of fear memory [48]. vHPC engram studies are still sparse, but seem to indicate that the activation of vHPC engrams can also drive valence-related behaviors: artificially reactivating vHPC cells active during encoding enhances behavioral expression of fear or reward place preference during

Box 1. Intrinsic and extrinsic hippocampal anatomical connectivity

Anatomical studies have revealed distinct connectivity patterns along the dorsoventral axis of the rodent hippocampus and the brain structures of the valence-processing network mentioned in this review. Unless specified, these connections are glutamatergic. There are bidirectional connections all along the dorsoventral axis with the thalamic nucleus reuniens [156], thus considered the main relay between the hippocampus and cortical areas. However, the mPFC receives direct input from the intermediate and vHPC [149], and has also marginal connections with the dHPC [145,146].

The NAc, part of the ventral striatum, receives inputs from all hippocampal subregions [131,133], but no projections from the NAc to the hippocampus have been identified. The VTA is a heterogeneous structure with intermingled dopaminergic, GABAergic, and a small population of glutamatergic neurons. The VTA sends sparse dopaminergic innervation to the whole hippocampus and glutamatergic projections to the dHPC which are thought to instruct the dHPC with reward signals [157]. The VTA does not receive direct hippocampal inputs [158]. The BLA, a core structure of the valence-processing network, has bidirectional connections with the ventral part of the hippocampus only [138] (see Figure 2 in the main text).

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

retrieval, through interactions with the BLA [49]. Hence, activation of either the dHPC or vHPC engrams can sustain the recall of contextualized emotional memories, likely through the recruitment of a larger engram spanning other valence-related structures. The limited connectivity of the dHPC and extended connectivity of the vHPC (Box 1) places the vHPC in a strategic position for the transmission and integration of dHPC contextual information with valence information.

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

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

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

Reactivation of hippocampal representations during sleep sustains memory consolidation

Memory consolidation is believed to occur partially during sleep through the off-line activation of patterns of neural activity previously elicited during learning, a phenomenon referred to as reactivation. Early reactivation studies in rats described that the firing rates or pairwise correlated activity observed during wakefulness in the dHPC were maintained during the following NREM sleep epoch [69,70]. It is now known that the temporal order of place cell firing can be conserved during reactivation, replaying entire trajectories during NREM following exploration [71,72]; this type of sequence reactivation is called replay [73–75]. Hippocampal reactivation preferentially occurs during hippocampal sharp wave-ripple complexes (SWRs) generated by the synchronous,

spontaneous activation of CA3 pyramidal neurons propagating to the CA1 region [76]. SWRs are believed to enable a decrease in the synaptic strength of irrelevant neuronal connections by promoting network long-term depression (LTD) [77], and the strengthening of relevant neuronal connections through selective long-term potentiation (LTP) [78], effectively enhancing the signal-to-noise ratio and therefore supporting memory consolidation [79]. In rats, the blockade of dHPC SWRs during postlearning NREM sleep, which concomitantly silences hippocampal activity and therefore the associated reactivation, impairs spatial memory consolidation [80,81]. On the contrary, the selective sparing of reactivation associated with an environment by suppressing all other synchronized events including reactivation of a second environment induces a learning impairment restricted to the suppressed environment [82]. The indirect suppression of dHPC SWRs during NREM sleep also impairs CFC in mice [83]. NREM sleep SWRs and reactivation in the dHPC thus sustain spatial memory consolidation.

How does emotional valence influence reactivations? During sleep ripples, stimulating dopaminergic inputs to the dHPC increases pairwise reactivation [84], suggesting an influence of valence or salience on sleep replay [85]. Artificially pairing place-cell activity during sleep with middle forebrain bundle (MFB) stimulations, thought to be intrinsically pleasurable through the activation of dopaminergic fibers, induces subsequent reward-related behavior toward the associated place field locations [86]. Thus, the activation of the dopaminergic system during sleep directly influences spatial memory consolidation, but the effect of valence on sleep reactivation is likely initiated during the encoding phase, a process conceptualized as emotional tagging [87]. Indeed, a study in rats underscored a preferential role of hippocampal replay for the consolidation of large rewards compared with small ones during a 2-h delay period between acquisition and retrieval [88]. Dopamine release is modulated by reward, aversive stimuli, salience, uncertainty, and novelty [89], and mediates hippocampal synaptic potentiation and neuron excitability [90], potentially enhancing the hippocampal representations of relevant locations and influencing the replay content of awake SWRs occurring during nonexploratory states of wakefulness [73,91,92]. Awake ripples and reverse replay are enhanced by the presence of reward [93,94], and awake replay will preferentially represent trajectories leading to a reward [95] (but see [96]). Replay has been detected during the avoidance of a shock zone [97], suggesting that it might sustain aversive memory retrieval. Finally, place cells that remap in a spatial avoidance task increase their participation in awake ripples during training [98], suggesting a link between the integration of aversive elements into the hippocampal representation and its immediate preferential processing. Another parameter to consider is that animals will avoid an aversive zone, and spend more time around rewarded areas, effectively reducing or increasing, respectively, the activity of the corresponding place cells, which could directly affect later reactivation. The acute stress triggered by an aversive experience could also influence reactivation, as suggested by the fact that repeated restraint stress decreases CA1 pyramidal activity, but increases participation in SWRs during wake and sleep [99]. Of note, chronic stress might have longer-term deleterious effects on memory, which differ widely from those of acute stress [100].

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

Neural oscillations coordinate the hippocampus and other valence-processing structures

Theta oscillations during encoding and retrieval

Various models of contextual emotional learning involve the hippocampus in combination with other valence-related structures. CFC is the canonical model for contextualized aversive memory; that is, the association of a specific context with an aversive stimulus, usually a footshock, in the context of rodent studies. CFC requires both the dHPC, believed to process the context, and the BLA [101], one of the core structures of the network processing fear and anxiety [102], including fear memory. Conditioning an animal to a simple auditory cue does not appear to require the hippocampus, suggesting that the hippocampus and the BLA interact to integrate aversive with context information. In addition, the mPFC, which has limited connectivity with the dHPC, is involved in the control of the expression of conditioned fear [103]. Observational fear learning (OFC) is a complex behavior that involves context, valence, and social processing. Animals having experienced shocks in a given context exhibit freezing when watching a conspecific experiencing the shock. The initial formation of the memory trace of the context in the dHPC is required and drives the formation of a memory trace in the BLA. A study in mice has shown that the expression of OFC involves the vHPC and BLA [104], and highlights the joint involvement of both the dHPC and vHPC in processing memories involving context and valence, in coordination with other structures of the network, in this case, the BLA [64]. What are the neural mechanisms underlying these interactions? Oscillations are believed to synchronize neural activity within and across structures, and phase-locking (i.e., the firing of neurons at specific phases of the LFP oscillation) is a marker of this synchronization. Within the hippocampus during exploration and movement, theta paces place-cell activity, organizing the neuronal assemblies that will later be reactivated during sleep [25]. The peak and troughs of the theta rhythm are favorable to LTP and LTD, respectively, in awake and anesthetized animals [105–107]. Coordination in the theta band between the dHPC, the amygdala, and the mPFC correlates with the acquisition and retrieval of cued and CFC [108–111]. Of note, however, the theta band as defined in these publications potentially overlapped with the 4-Hz coordinated oscillation between the mPFC and amygdala that was later shown to control the expression of freezing [112,113]. In a study in mice, manipulating theta power in the vHPC was shown to modify the amount of exploration of odor predator-associated zones [114]. In addition, theta coordination between the vHPC and mPFC is increased in anxiogenic environments [115], and mPFC units responding to aversive or safe stimuli in anxiogenic tasks are strongly locked to vHPC theta, but not dHPC theta [116]. In another study, optogenetic stimulation at theta frequency of vHPC inputs to mPFC activity was associated with increased synchronicity between vHPC theta and mPFC spiking activity and enhanced avoidance behavior in the elevated plus-maze [117]. Theta oscillations during wakefulness thus emerge as a key mechanism for the synchronization of dHPC and vHPC with other structures sustaining innate and learned emotional behaviors.

Theta oscillations during REM sleep

Theta oscillations are also a hallmark of REM sleep. Studies in humans point towards a role for REM sleep in emotional memory consolidation [118] (but, see [119]). The underlying physiological mechanisms, however, are still largely unknown (see Outstanding questions). Studies in mice and rats have shown that selective REM sleep deprivation or inhibiting theta oscillations during postlearning REM induces contextual memory impairments [120,121]. However, classical, NREM-sleep-like dHPC reactivation has not yet been widely found during REM sleep [122], although there are some similarities between awake and REM sleep neuronal patterns [123,124]. Theta power in the dHPC during a REM-sleep episode correlates with an increase in the synchrony and firing rate of pyramidal cells during the SWRs of the following NREM epoch [125], suggesting that REM sleep might initiate plastic changes implemented during

NREM sleep. Aversive learning and extinction trigger changes in theta synchronization during REM across the dHPC, vHPC, BLA, and mPFC, especially in the dHPC–BLA coherence and vHPC–LA (lateral amygdala) phase shift [126,127], but in the absence of structured dHPC–BLA reactivation [128]. Hippocampal theta oscillations are traveling waves [129], the propagation of which across the dorsoventral axis [29] could mediate communication between the dHPC, vHPC, and the rest of the valence-related network through the vHPC connections. Indeed, theta synchronization between the dorsal and vHPC increases during the retrieval of trace fear conditioning [130]. Thus, further investigation is required to elucidate how changes in the organization of neural activity by REM theta oscillations within the hippocampus and across structures might contribute to the consolidation of experiences of different emotional valence and salience.

SWRs during nonexploratory wakefulness and NREM sleep

During training on a rewarded spatial task, dorsal and ventral SWRs activate distinct and opposing patterns of NAc spiking. NAc neurons responding to dHPC SWRs show more location and reward-related activity [131], and the coupling between dHPC and NAc neurons encoding a location associated with cocaine administration increases during wakefulness and sleep [132]. This suggests that awake and sleep SWRs originating from the dHPC versus vHPC could play distinct roles in the integration of space and valence information, supported by the respective anatomical connections between the dHPC, vHPC, and NAc [133]. Reward-responsive ventral tegmental area (VTA) neurons activate synchronously with dorsal hippocampal reactivation events of appetitive spatial experience during quiet wakefulness [134], and ventral striatum reward-related cells also reactivate in coordination with dHPC place cells during SWRs [135,136], probably primed by the coordination of dHPC-striatal neural activity by theta phase precession during learning [137]. Thus, interactions between the dHPC and other structures related to reward processing might sustain the consolidation of place-reward associations [86]. On the other end of the valence spectrum, the dHPC–BLA pairwise representation of an aversive experience is reactivated during NREM sleep SWRs [128]. In the absence of direct connections between the dHPC and BLA [138,139], these joint reactivations necessarily involve at least one relay structure, potentially the vHPC. Indeed, inactivating vHPC neurons after training impairs the consolidation of contextual fear memory [140], potentially by impairing the vHPC NREM reactivation of stimulus-related activity which is modulated by BLA inputs [42]. During NREM sleep following fear conditioning, there are also multistructural reactivations involving the vHPC, BLA, and infralimbic part of the mPFC associated with high-frequency oscillations in vHPC and BLA and modulated by cortical slow waves [141]. Because they propagate along the dorsoventral axis [142], SWRs are a likely candidate for binding dorsal and vHPC activity during NREM sleep. There is a progressive decrease in the dorsoventral coordination of SWRs along the dorsoventral axis, reaching marginal coordination between the most dorsal and ventral zones (Figure 2). However, this has only been examined in the absence of previous spatial or emotional learning, and the need for joint consolidation of spatial and valence information could affect dorsoventral SWR coordination.

In the cortex, NREM sleep is characterized by thalamocortical spindles and slow oscillations arising from the synchronized alternation of periods of high activity and quiescence in cortical neurons, referred to as up and down states. Systems consolidation involves a transfer of information from the hippocampus to cortical areas and is mediated by the temporal organization of neural activity by dorsal hippocampal SWRs, thalamocortical spindles, and cortical slow oscillations [143]. Notably, the artificial enhancement of the coordination between dHPC ripples and down-state-spindle complexes in the mPFC improves memory consolidation [144]. Thus, dHPC–cortical coordination is a crucial mechanism for memory consolidation despite the limited anatomical connections between the dHPC and mPFC [145,146]. The coordination between ventral ripples

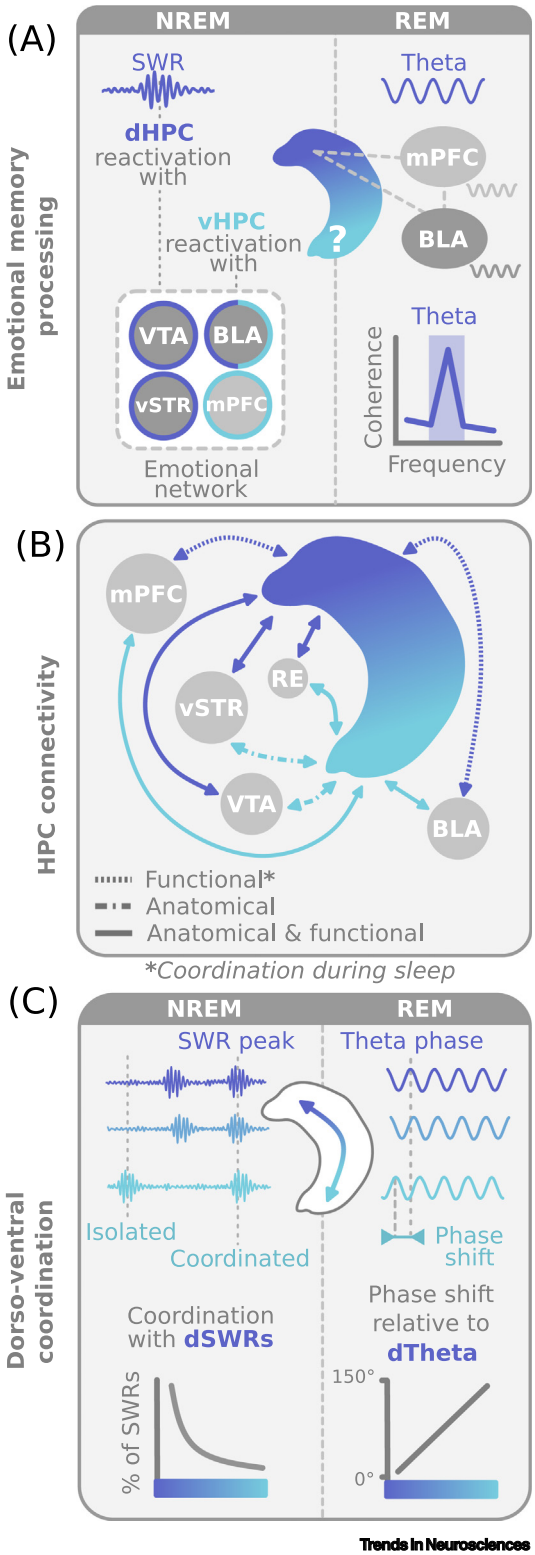

Figure 2. Anatomical-functional characteristics throughout the hippocampus during sleep. (A) The hippocampus is involved in emotional processing during sleep. During NREM sleep or quiet wakefulness, and preferentially during ripples (SWRs), following reward/aversive learning, there are coordinated reactivations between the dHPC and valence-processing structures: vSTR, VTA, and BLA [128,135,136]. The vHPC was shown to reactivate with the BLA and the mPFC [141]. During REM sleep following aversive learning, theta coherence increases between dHPC, BLA, and the mPFC [126] (B) The observations summarized in (A) can only be partially explained by the anatomo-functional connectivity of the hippocampus along the dorsoventral axis. Functional connections indicate that oscillatory or neuronal coordination between the hippocampus and the other structures represented in the graph have been described during sleep and correlated with memory formation. (C) Oscillations propagating along the hippocampal dorsoventral axis during sleep could mediate the transfer of contextual and emotional information along the longitudinal axis and towards the other structures of the emotional network. During NREM, dorsoventral SWRs coordination decreases along the axis, and most vHPC SWRs are isolated from dorsal ones. During REM, theta oscillations travel across the dorsoventral axis and their phase shifts [29,142]. Abbreviations: BLA, basolateral amygdala; dHPC, dorsal hippocampus; mPFC, medial prefrontal cortex; NREM, non-REM; RE, nucleus reuniens; REM, rapid eye movement; SWR, sharp wave-ripple; vHPC, ventral hippocampus; vSTR, ventral striatum; VTA, ventral tegmental area.

and cortical/thalamic slow waves also increases after contextual fear learning, as well as ventral ripple events phase-locking to cortical/thalamic spindles, albeit uncorrelated with memory performance at retrieval [147]. The thalamic nucleus reuniens is emerging as a relay structure for the coordination between the ventral and intermediate hippocampus and the mPFC [147,148]. To our knowledge, only one study has established the functional implication of the monosynaptic connections from the ventral and intermediate hippocampus to the mPFC during memory consolidation [149]. Systems consolidation of emotional memories could thus involve direct or indirect coordination between the vHPC and cortical areas, and/or triple coordination of dorsal and vHPC SWRs with cortical oscillations.

Concluding remarks and future perspectives

The features of neurons along the dorsoventral axis of the hippocampus display a gradient from mostly spatial to mostly emotional, and the neural representations in the dHPC and vHPC are involved in the expression of contextual and valenced memories through their connectivity with other valence-related structures. Spatial memories are consolidated during sleep through neural reactivation and the organization of neural activity by NREM sleep SWRs and REM sleep theta oscillations. Although these phenomena have been mostly studied in the dHPC, there are preliminary indications that the same principles could hold for emotional memory consolidation in the vHPC. However, most memories are complex and combine contextual and emotional information. How is the contextual information transferred to structures that lack direct connectivity with the dHPC? We propose that changes in the coordination between the dorsal and vHPC through theta oscillations and SWRs might underlie the gating of contextual information for their integration with valence information processed in the rest of the network, including the BLA and mPFC. To directly test this hypothesis and more generally refine theories of the processing of emotional information, the physiology of the vHPC and the connections of this area with the rest of the valence network deserve further investigation. For example, vHPC inputs to the mPFC are anatomically and functionally segregated according to the depth of the projecting neurons in the pyramidal layer: superficial neurons are preferentially connected to PFC inhibitory interneurons and promote exploration, whereas deeper neuronal populations project to PFC pyramidal neurons and fast-spiking interneurons, and promote avoidance [59]. In the dHPC, CA1 pyramidal neurons have different spatial properties depending on their depth [150,151], influencing their recruitment into slow oscillations, SWRs, reactivation, and REM theta [146,152,153]. Can similar gradients be found in the vHPC for spatial or valence-related properties? Crucially, it is still unknown whether vHPC neuronal assemblies reactivate during vHPC ripples. If so, would the content of the reactivation be exclusively valence-related or exhibit a mix of valence and contextual information? Would vHPC reactivation be coordinated with contextual reactivation in the dHPC? Overall, a better understanding of how ventral and dorsal hippocampal sleep SWRs and reactivation differentially recruit other brain areas would help refine their respective roles during emotional memory consolidation. Of note, a longstanding bias has restricted research on memory consolidation to mostly males. While it is unclear how sex and hormonal variations affect spatial memory, it is known that there are sex-dependent differences in fear conditioning [154] and that hippocampal plasticity is susceptible to hormonal changes [155]. Because women are more susceptible to post-traumatic stress disorder (PTSD) and anxiety disorders, future research on emotional memory consolidation in rodent models should strive to balance the sexes and carefully examine potential sex differences. Finally, there is still a lack of both causal and physiological evidence supporting the involvement of ventral theta oscillations during REM in memory consolidation. Overall, the vHPC holds significant potential as a focal point for future research on emotional memory consolidation during sleep, with particular attention to be paid to the pertinent anatomical connections between neural circuits.

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 dorsoventral axis in the absence of consolidation requirements (i.e., previous learning or exploration). How is the dorsoventral coordination during sleep affected by the valence of the preceding experience? What are the anatomical underpinnings of disconnection versus coordination? Is the mechanism intrahippocampal, 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 sleep for dHPC-mediated spatial processing?

How does emotional valence during encoding influence sleep reactivation in the dHPC? 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?

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Declaration of interests

The authors declare no competing interests.

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