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Overnight neuronal plasticity and adaptation to emotional distress

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Abstract

Expressions such as ‘sleep on it’ refer to the resolution of distressing experiences across a night of sound sleep. Sleep is an active state during which the brain reorganizes the synaptic connections that form memories. This Perspective proposes a model of how sleep modifies emotional memory traces. Sleep-dependent reorganization occurs through neurophysiological events in neurochemical contexts that determine the fates of synapses to grow, to survive or to be pruned. We discuss how low levels of acetylcholine during non-rapid eye movement sleep and low levels of noradrenaline during rapid eye movement sleep provide a unique window of opportunity for plasticity in neuronal representations of emotional memories that resolves the associated distress. We integrate sleep-facilitated adaptation over three levels: experience and behaviour, neuronal circuits, and synaptic events. The model generates testable hypotheses for how failed sleep-dependent adaptation to emotional distress is key to mental disorders, notably disorders of anxiety, depression and post-traumatic stress with the common aetiology of insomnia.

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Introduction

The emotional memory trace

Sleep and emotional memory

Conclusion, critical evaluation and summary

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Introduction

Memories make us who we are. It, therefore, matters what we remember and forget of our past experiences. A well-studied factor in determining what we remember is the level of emotional, visceral distress that was present during the experience or elicited by it. High distress facilitates remembering of factual information^{1–3}. Such memories have commonly been referred to as ‘emotional memories’, even if they are no longer experienced as emotional, but rather as only factual, at the time of recall. This phenomenon might, therefore, better be called ‘initial emotion-modulated memory’.

It is, however, not only the factual content of memories that makes us who we are. Equally important is the emotional, visceral distress we may experience again upon remembering the past experience, or upon being re-exposed to the same or a similar experience. One might call this phenomenon ‘memory-modulated emotion’. Whereas some are capable of revisiting just the facts of a gruesome experience, others cannot do so without re-experiencing the distress the experience initially elicited.

Brain mechanisms of initial emotion-modulated memory have extensively been studied, as reviewed below in ‘[The emotional memory trace](#)’. More recent studies have addressed the factors that determine whether the factual memory can be reactivated without eliciting emotional, visceral distress. As reviewed in the section ‘[Sleep and emotional memory](#)’, sleep has emerged as a major factor. How is it possible that we can wake up less distressed about issues that seemed so problematic prior to sleep? The importance of sleep for overnight memory processes has been shown across three major levels of neuroscience: the behavioural and brain-systems level, the neuronal-circuit level, and the cellular–synaptic–molecular level. This perspective integrates findings across these levels and presents a theoretical framework of the neuronal molecular processes that support the adaptation of brain circuits required to subjectively feel better in the morning.

The scope of this Perspective is to discuss the iterative mechanisms by which overnight cellular and systems plasticity adaptively consolidates the parts of emotional memory traces that represent factual information, while weakening or suppressing parts of the memory trace that represent the emotional distress that occurred with the experience. That is not to say that wakefulness does not support memory consolidation or that some studies did not find a differential effect of sleep versus wake on consolidation of some types of memory^{4–8}. Furthermore, sleep also has a broad effect on both positively and negatively valenced affect and mood⁹. However, the memory trace we refer to consists of the narrative about a past experience of an explicit episode. These explicit, episodic memory traces are placed within a network of semantic facts about oneself and the world that form schema and also include implicit, unconscious modifications by our sensory and motor systems, and changes in behavioural inclinations, all of which are considered implicit, procedural components of memory. Although this Perspective focuses on negatively valenced emotional episodic memories, these memory traces do not exist in isolation; both explicit and implicit components of memory interact.

The overnight neuronal plasticity that is important for emotional resolution includes strengthening of some memory circuit components and targeted weakening of others. The global homeostatic downscaling of synapses during sleep¹⁰ is another sleep-dependent mechanism, which is not inconsistent with the parallel process of this circuit-specific remodelling we focus on here^{11,12}. Indeed, both processes are addressed where applicable.

Recent research has shown causal involvement of the noradrenergic system in arousals from sleep^{13,14}, and its periodic tonic inactivity

during sleep corresponds to permissive windows wherein rapid eye movement (REM) sleep and non-REM (NREM) sleep spindles, which are important for overnight memory consolidation^{14–16} and overnight adaptation of limbic brain responses¹⁷, can occur. During consolidated periods of inactivity of the locus coeruleus (LC) that occur specifically during sleep, downstream noradrenaline (NA) can slowly drop to levels that never occur during wakefulness or slow-wave sleep (SWS). Whether NA is high, is at its normal restful wake or SWS level, or becomes very low during consolidated sleep-specific periods of LC inactivity can make a huge difference to the outcomes of synaptic plasticity processes¹⁸. In this Perspective, we will focus on the effects of NA on plasticity processes that are relevant to emotional memory, including the effects of high NA during the initial distressing experience and those of subsequent sleep-specific periods of low NA on overnight consolidation and adaptation of emotional memories. Other neurotransmitter systems will be mentioned when their unique contributions to the model come into play.

The review is structured as follows. First, the definition of ‘emotional memory consolidation’ is provided with further detail on how emotional arousal, and NA in particular, facilitates memory consolidation across decreasing levels of scale: experience and behaviour, neuronal circuits and synaptic events. Subsequently, in reverse sequence, we travel back through these orders of scale to discuss the effects of sleep on changes in the molecular makeup of synapses, on changes in limbic, salience and autonomic circuits, and ultimately on adaptation of subjective emotional distress.

The emotional memory trace

Systems-level memory consolidation

How can it be that, after memory consolidation, factual information is better remembered if experiences are emotional, whereas at the same time the emotional distress that was part of the experience does not re-emerge? During encoding, emotional arousal modulates the responsiveness of attentional, salience and sensory brain networks to stimuli, making it more probable that the most salient details of emotional experiences will be encoded into a memory trace^{1–3}. An emotional memory trace can be defined as the set of synaptic connections between engram neurons in distributed brain networks that represent the factual information, context, and sensory, interoceptive, arousal and emotional aspects of experiences through synchronized activity and modulation of intrinsic cell excitability^{19,20} (Fig. 1a). During systems consolidation, memory traces undergo not only stabilization but also transformation, including (1) the integration of the acquired memory trace with existing internal models of oneself and the world (also termed memory schemas²¹), which are mostly established in cortical networks²²; and (2) gradual adaptation of limbic representations^{23,24}. Whereas the word ‘consolidation’ may suggest the strengthening of synaptic connections, the transformation it describes includes weakening of connections as well^{25,26}. This highlights a first important principle: a memory trace is distinguished as much by which neurons are not connected as by which neurons are connected.

The mechanisms of selective prioritized consolidation and adaptation of emotional memories find their roots in the synaptic and behavioural tagging hypotheses^{27,28}. The neuromodulatory effects of a salient stimulus or an emotional context lead to translation of plasticity-related proteins (PRPs) that are necessary for long-lasting consolidation. These PRPs can – within a critical time window – also induce strong consolidation of otherwise neutral yet specific aspects of a memory trace that were initially weakly encoded but were ‘tagged’

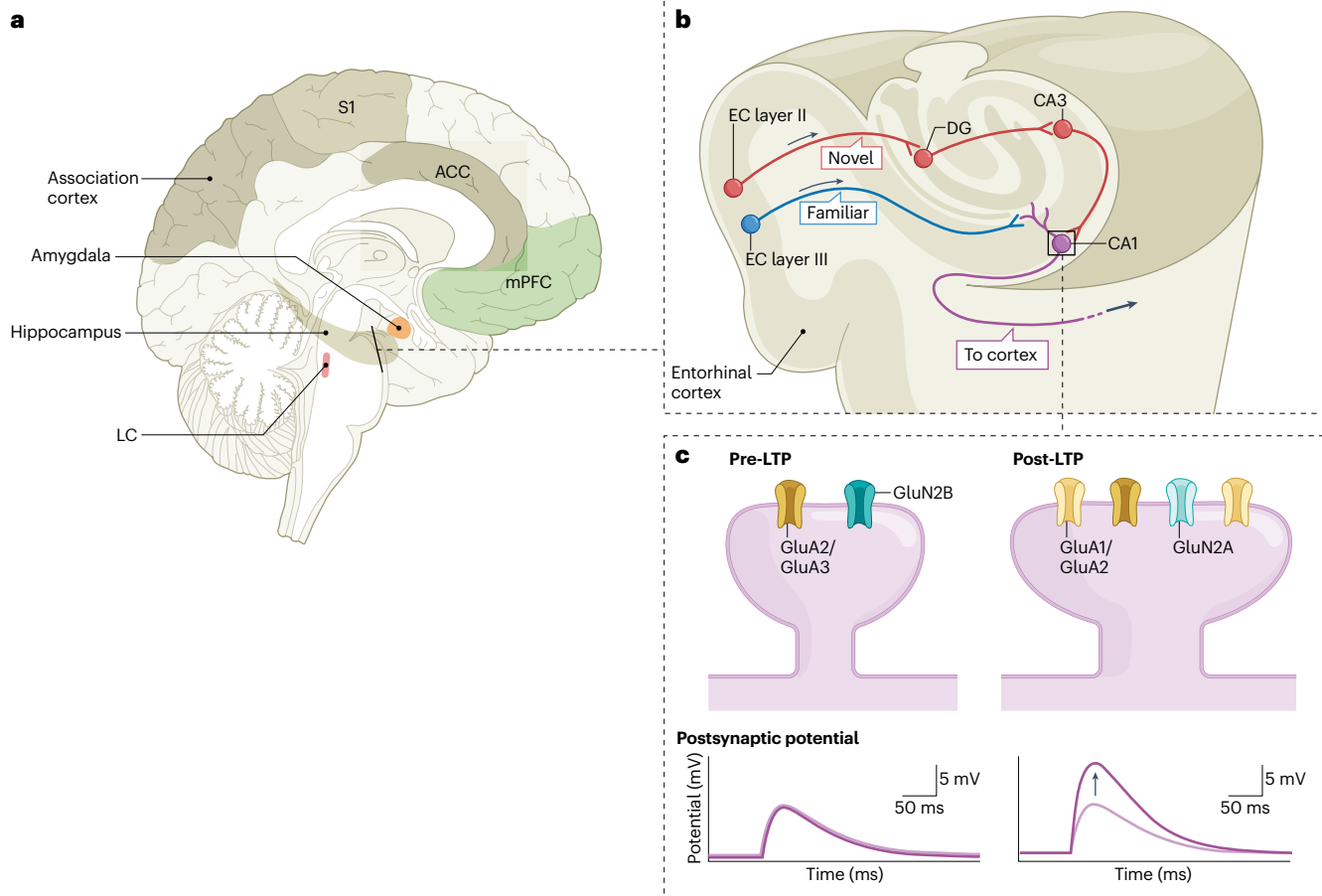


Fig. 1 | The systems, circuit and molecular levels of a memory trace.

a, Distributed neuronal systems encode emotional experiences. Afferent information is processed by the primary somatosensory cortices (S1) and refined via the association cortices. The anterior cingulate cortex (ACC) and other regions in the salience network process interoceptive information, whereas the locus coeruleus (LC) and amygdala are implicated in arousal and emotional distress. The medial prefrontal cortex (mPFC) is implicated in a broad range of cognitive evaluation and behavioural response selection. **b**, The entorhinal cortex (EC) and subfields within the hippocampus. The EC is the main gateway

into the hippocampus wherein novel information is relayed onto the perforant pathway (especially under noradrenergic neuromodulation; red), whereas the temporoammonic pathway (blue) encodes familiar information in the absence of noradrenaline. CA1 is the main output region with projections to the cortex. **c**, Differences between synapses before (left) and after (right) induction of long-term potentiation (LTP). LTP increases postsynaptic potentials through enlargement of the synapse, addition of GluA1 or GluA2 AMPA receptors and substitution of GluN2B with GluN2A NMDA receptors. DG, dentate gyrus; Glu, glutamate. Panel **b** modified with permission from ref. 244, Elsevier.

through association with the salient stimulus or emotional context^{29,30}. For example, during encoding of a contextual fear memory, input from the hippocampal–entorhinal complex and basolateral amygdala can establish prefrontal engram cells that are initially weakly encoded, but the prefrontal engram cells gain structure and function after consolidation to the extent that activity in these cells is sufficient for remote memory recall in rodents³¹. Importantly, following extinction learning, memory consolidation in ventromedial prefrontal engram cells is also required for successful fear-extinction recall – that is, to suppress fear expression³² through basolateral amygdala-mediated inhibition of the central nucleus of the amygdala (the main output region that drives the fear response)³³. Furthermore, human studies have shown that the ventromedial prefrontal cortex is involved in transformation of the source memory trace into an integrated memory schema^{34,35}, a process linked with sleep-dependent

memory consolidation (further discussed in ‘Sleep and emotional memory’)³⁶. It is, therefore, theorized that the tagging mechanism primes emotional memory traces for reactivation and consolidation during sleep³⁷ and that it facilitates the integration of neutral and factual information about the cues and context into memory schema, aiding the habitualization of response patterns³⁸ and top-down control over the emotional response^{24,39} (see ref. 33 for a detailed review of the prefrontal–amygdalar circuit involved in top-down control). This leads to our second important principle: although consolidation of emotional experiences is prioritized, successful adaptive consolidation also prevents re-emergence of the distress initially experienced.

Consolidation of emotional experiences is, however, not always successfully adaptive. It can happen that memory consolidation does not prevent re-emergence of the distress initially experienced, or in the worst cases can even result in increased distress. How can adaptive

consolidation processes turn into maladaptive ones? Clues can be derived from studies on emotional plasticity that have shown that the neuromodulatory milieu may be crucial⁴⁰. Experimental manipulation of the neuromodulatory context (for example, exogenous administration of NA into the brain) following distressing experiences leads to continued fear expression in rodents^{41,42} and impaired integration into cortical memory schema in humans⁴³. Moreover, when stressors are exceedingly intense or these neuromodulators are experimentally enhanced, it can impair consolidation of the contextual aspects of memory and instead increases generalized fear expression, for example, to peri-contextual cues that are not directly associated with the stressor^{41,44}. Such generalization and maladaptive consolidation of environmental context is characteristic of anxiety disorders and of post-traumatic stress disorder^{45,46}. This highlights a third important principle: the intensity of emotional distress associated with the memory trace is probably an important factor for the time it takes to adapt or, in cases of lasting traumatic distress, to fail to adapt an emotional memory.

Circuit-level emotional memory encoding

Convergent neuronal activity induced by a distressing stimulus activates the noradrenergic LC ascending arousal system within tens of milliseconds via collateral innervation from all sensory modalities^{47,48}. The LC first activates the nearby reticular activating system in the brainstem, whose myelinated axons quickly alert the brain to arouse and attend to the incoming stimuli. The arousal pathway includes activation of the hypothalamus, thalamus and neocortex and invokes the emotional limbic system (for example, the hippocampus and amygdala) as well as the salience circuit (for example, the insula and cingulate cortex)⁴⁹ (Fig. 1a). The unmyelinated fibres of the LC deliver NA to these higher brain targets in the cognitive and emotional circuits at about the time the information is being evaluated within these circuits⁵⁰. This initial neuronal representation of the experience is encoded by modulation of spike timing-dependent plasticity through cross-frequency coupling of neuronal oscillations across brain regions^{51–55}; for example, primary somatosensory cortices, association cortices and entorhinal cortex (EC; a gateway region into the associative memory structure called the hippocampus)^{56,57}. Thus, the formation of the initial memory trace, boosted by the LC, includes nodes representing facts and nodes representing emotional arousal and salience.

Characteristic of an emotional event is that there is a prediction error between what is expected on the basis of cues and context and the actual outcome⁵⁸, that is, the outcome is unexpected and has a high degree of novelty. Familiar stressors instead induce an adapted hypothalamic–pituitary–adrenal axis response in rats⁵⁹. Furthermore, although human brain activation patterns in response to novel emotional stimuli include limbic brain regions, recall of remote emotional memories does not, but only in normal sleepers⁶⁰. In this latter study, patients with insomnia showed brain activation patterns and correlated autonomic responses similar to those of people experiencing novel distress, in particular in the anterior cingulate cortex (ACC), which is known to be involved in prediction error⁶¹. For these reasons, one important field of research for understanding how novel emotional memory traces are consolidated into adapted familiar ones is that of hippocampal remapping.

During waking learning, the EC and hippocampus work together to assess whether the stimulus information is novel, necessitating modification of existing memory traces, or whether the information is familiar, that is, already consolidated. This is achieved by the composition of a circuit described by Vinogradova⁶² as the novelty-encoding

trisynaptic perforant pathway and the familiarity-encoding temporoammonic pathway (Fig. 1b). Novel information is relayed through the perforant pathway, activating the dentate gyrus, and is amplified in the CA3 region. Already established ‘familiar’ memories are also relayed through the trisynaptic pathway. But in the absence of bursts of activity in the LC to weight the trisynaptic circuit, the consolidation-strengthened temporoammonic pathway from EC layer III to the CA1 region can dominate CA1 activity patterns^{62–65}. These different patterns of hippocampal subfield interactions can, thereby, distinguish between novel and familiar stimuli. High levels of acetylcholine and NA during wakefulness amplify encoding in novelty circuits by enhancing the synaptic strengthening effects of synchronous co-activity and by enhancing responses to sensory and perceptual input in the dentate gyrus and CA3 areas of the hippocampus^{66–69}. LC activity strongly inhibits the familiarity pathway through α 2-adrenergic receptor-mediated inhibition of EC layer III pyramidal neurons^{69,70}. In addition to the activation of the LC that strong external sensory inputs (for example, startling sounds or physical force) provide, LC activity is also increased when emotional limbic and salience networks, hypothalamic areas and the orexin (hypocretin) arousal system have assigned salience to an external input or to internally generated thoughts or memory recall, as these forebrain areas project excitatory inputs back to the LC, and experimental stimulation of amygdalar afferents to the LC induces anxiety-like behaviour in mice^{71–73}. Thus, NA biases the hippocampal circuit to encode novel, high-arousal stimuli over familiar ones, and it amplifies glutamatergic excitatory signalling in brain areas processing the prioritized representations^{74,75}, altogether strengthening the novel memory trace⁷⁶.

Cellular and synaptic plasticity

At the cellular and synaptic level, memory traces are created through long-term changes in the synaptic efficacy of the connections in neuronal ensembles called memory engrams. The release of NA has prominent effects on the capacity to induce and maintain synaptic plasticity in engram neurons. Synaptic plasticity processes can be presynaptic, for example, through a change in the probability of neurotransmitter release, or can be of postsynaptic origin, for example, through a change in the number or type of neurotransmitter receptors^{77–79}. A form of synaptic plasticity that is known to contribute to memory encoding at excitatory synapses is long-term potentiation (LTP), which rapidly increases the strength of existing synapses (Fig. 1c). Postsynaptic LTP depends on coincidence detection by NMDA-type glutamate receptors (NMDA receptors) at synapses, and it is expressed by the addition of AMPA-type glutamate receptors (AMPA receptors) at the postsynaptic membrane^{80,81}. The majority of AMPA receptors in excitatory neurons consist of either subunits GluA1 and GluA2 or GluA2 and GluA3 (ref. 82). Whereas GluA2/GluA3 heteromers traffic into synapses independently of synaptic activity, GluA1/GluA2 receptors are inserted into synapses upon LTP, leading to spine enlargement^{80,83}. LTP also leads to changes in NMDA receptor subunit composition: GluN2B-containing NMDA receptors are exchanged for those containing GluN2A at potentiated synapses^{84,85}, which prevents further modification of the memory trace, thereby acting as a stabilizer of synaptic changes⁸⁶.

When NA levels are high, LTP is facilitated by β -adrenergic receptor activation, which increases intracellular cAMP. For instance, high cAMP levels promote activity of NMDA receptors, particularly those containing subunit GluN2B (ref. 87), and a rise in cAMP increases synaptic currents through Ras-mediated activation of GluA2/GluA3 ion channels⁸⁸. In addition, NA triggers the phosphorylation of GluA1 subunits, which promotes their trafficking into synapses, thereby lowering

the threshold for LTP (refs. 89–91) (Fig. 2). In summary, LTP is facilitated by NA and leads to enlarged synapses that are enriched for GluA1 and GluN2A, whereas synapses devoid of LTP are relatively small and enriched for GluA3 and GluN2B (refs. 83,92). These changes in synaptic AMPA receptor and NMDA receptor subunit composition can be used as PRPs characteristic of the occurrence of postsynaptic LTP at excitatory synapses.

NA also promotes the maintenance of LTP. Whereas early-phase LTP (up to ~3 h) is independent of protein synthesis, late-phase LTP depends on expression of PRPs such as Arc, which is stimulated by NA (ref. 93) and by cAMP signalling⁹⁴. Arc is expressed in memory engram neurons and, interestingly, can function as an ‘inverse synaptic tag’, as it is predominantly located at non-potentiated spines^{95–98}. At these spines, Arc is capable of removing AMPA receptors, thereby lowering the strength of synapses that are not involved in the memory trace, while keeping those involved in the memory trace intact^{98–100}. Another important reason why late-phase LTP would depend on protein synthesis is that learning involves not only modulating existing synapses but also the creation of new ones. In vivo monitoring of structural plasticity under baseline conditions revealed that a proportion of synapses are dynamic, with balanced gains and losses¹⁰¹. A higher gain in spines is observed in cortical neurons upon learning a new task¹⁰², in lateral amygdala neurons upon forming an associative memory¹⁰³, and in hippocampal neurons upon the induction of LTP (ref. 104). The observation that β -adrenergic activation increases both LTP and the number of spines in the hippocampus demonstrates that NA is capable of stimulating this structural plasticity^{105–107}.

Synaptic connections between components of a memory trace can also be weakened through either of two processes called depotentiation and long-term depression (LTD), which are the proposed mechanisms for adjusting or forgetting a memory^{108–110}. LTD occurs when NMDA receptors are activated in the absence of postsynaptic depolarization^{77,111}, for instance, at synapses receiving non-coinciding inputs or at synapses that are hyperpolarized owing to inhibitory tone. Postsynaptic LTD is expressed by the removal of both GluA1-containing and GluA3-containing AMPA receptors from synapses^{112,113}. When LTD is induced at synapses that were recently potentiated by LTP, this is

referred to as ‘depotentiation’, which uses partly different signalling cascades to selectively remove GluA1-containing AMPA-receptors from synapses¹¹⁴. NA, however, inhibits LTD and depotentiation through phosphorylation of GluA1 (refs. 89–91), which prevents the endocytosis of GluA1-containing AMPA receptors¹¹⁵. Thus, when levels of NA are low, the LTP–LTD plasticity balance would shift towards LTD and depotentiation. As consolidated REM sleep is characterized by both a low level of NA (refs. 14,116,117) and activation of limbic circuits^{118–121} even beyond their activity during wakefulness, this sleep stage could be highly suitable for prioritized depotentiation of the limbic synapses that represent the distressing part of an emotional memory trace, as will be discussed in the next section.

Sleep and emotional memory

Sleep is not a single homogeneous state of unconsciousness. It can be subdivided broadly into NREM and REM sleep, each with very different neurophysiological activity and neuromodulatory contexts that have unique consequences for processing emotional memory traces (Fig. 3), which are introduced first. This is followed by discussion of the effects of sleep on the molecular makeup of synapses and changes in limbic, salience and autonomic circuits that support or undermine adaptation of emotional distress.

Sleep states

During NREM sleep, firstly, hippocampal sharp wave–ripples of ~50–100 ms occur. They contain a compressed representation of the temporal order of activity during the learned event. Sharp wave–ripples are abundant during NREM sleep, when levels of acetylcholine are low¹²². Secondly, the ripples are often – but not exclusively – nested within thalamo-cortical sleep spindles (0.5–2.0 s oscillatory events in the frequency range of 11–15 Hz in humans and in a more variable range of 9–25 Hz in rodents)^{123–125}. Finally, sleep spindles are temporally coupled to cortical slow oscillations (<1 Hz) with significant memory performance improvement correlations at ~0.5–3.0 s after slow-oscillation up-states¹²⁶, although the preferred timing of this coupling may be dependent on the sleep stage and cortical region¹²⁷ and/or the frequency of the spindle (that is, fast versus slow spindles)¹²⁸. Importantly,

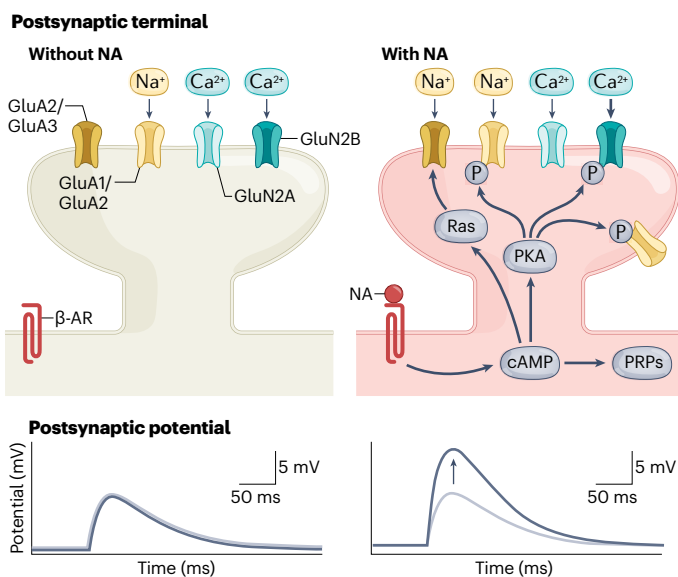


Fig. 2 | Increased synaptic communication through noradrenergic signalling.

A synapse under basal conditions without noradrenaline (NA, left) and under the influence of NA (right). NA activates β -adrenergic receptors (β -ARs), which trigger the production of cyclic adenosine monophosphate (cAMP). A rise in cAMP increases synaptic currents through Ras-mediated activation of GluA2/GluA3 ion channels. A rise in cAMP also activates protein kinase A (PKA), which phosphorylates the NMDA receptor subunit GluN2B, thereby increasing receptor permeability for calcium ions (Ca^{2+}). Phosphorylation of GluA1 by PKA promotes surface expression of extrasynaptic GluA1/GluA2 receptors. cAMP also promotes expression of plasticity-related proteins (PRPs), which are involved in late-phase long-term potentiation. Together, these effects lead to a lowered threshold for long-term potentiation and to prevention of long-term depression and maintenance of long-term potentiation. Na^+ , sodium ion; P, phosphate.

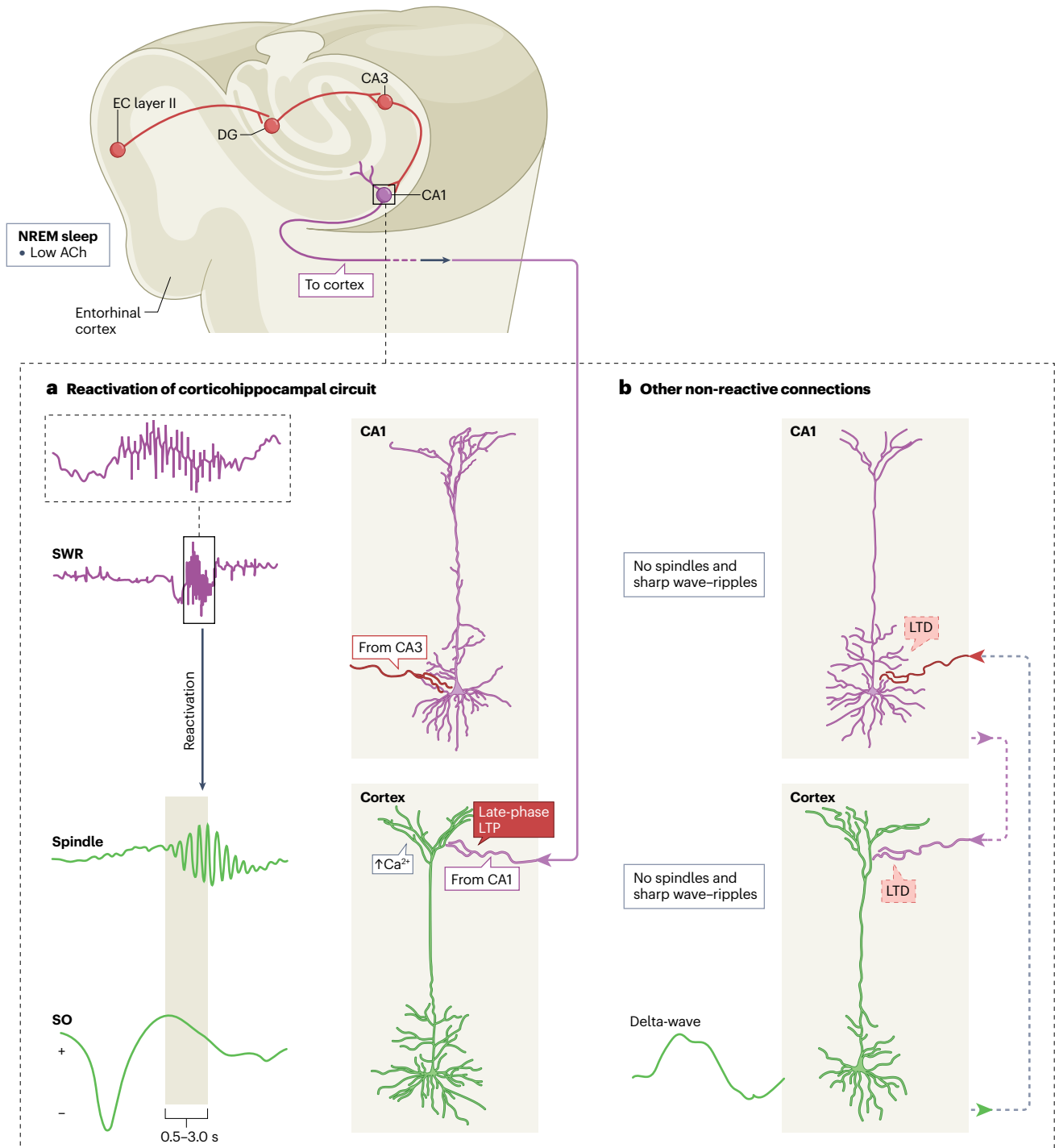


Fig. 3 | Memory trace consolidation through late-phase LTP inducing activity in cortico-hippocampal circuits. a. During non-rapid eye movement (NREM) sleep, the CA1 region (purple) generates sharp wave–ripples (SWRs) in response to activation by the CA3 and dentate gyrus (DG, red connections). These SWRs couple with thalamo-cortical spindles and cortical slow oscillations (green). This coupled activity provides strong excitatory gain at cortical synapses and a large influx of calcium (Ca²⁺), and is proposed to induce late-phase LTP, or at

least to prevent depotentiation, at the reactivated synapses. **b.** Conversely, long-term depression (LTD) and/or depotentiation occurs at other non-reactivated connections because these neurons are still repetitively activated at low delta frequencies, albeit at much lower-voltage postsynaptic depolarization (that is, no spindles and SWR), leading to weak Ca²⁺ influx triggering long-term depression and depotentiation. ACh, acetylcholine; LTP, long-term potentiation. Top image adapted with permission from ref. 244, Elsevier.

tonic LC activity and cortical NA levels show a periodic pattern at time-scales of ~30–100 s (refs. 13,14,16). Sleep spindles are also clustered at this timescale, but in an anticorrelated fashion, because their occurrence is suppressed by NA (refs. 15,16,129–131). Phasic LC activity falls silent 1–5 s before spindles are initiated, but it fires at the apex of the spindle^{15,116}. Interestingly, the LC also fires on the rising phase of the slow oscillation¹³². It has been proposed that this coupling between the hippocampus, thalamus and cortex modulated by tonic and phasic LC activity during NREM sleep can promote LTP among recently active synapses and/or prevent synaptic weakening^{132,133}.

REM sleep is characterized by a low level of NA (refs. 13,116,117) and high cholinergic neuromodulation¹²². Under these conditions, the hippocampus, amygdala and cortex generate theta oscillations¹³⁴ which couple with ponto-geniculo-occipital (PGO) waves^{135–137}, both of which are implicated in processing emotional memory^{134,138–141}. Recently, it has been shown that although some types of interneuron strongly inhibit hippocampal and cortical proximal dendrites, other types disinhibit the distal dendritic tree during REM sleep^{142,143} and during NREM sleep sharp wave–ripples, spindles and coupled slow oscillations^{144–146}, which could also have an important role in emotional memory consolidation¹⁴².

Finally, sleep is not continuous. Intrusive arousals and awakenings from sleep occur during the peaks of periodic cortical NA levels^{16,147}, which can have negative consequences for overnight memory consolidation¹⁵ and adaptation of limbic brain responses to recall of emotional memory¹⁷.

Synaptic plasticity during sleep

How the molecular makeup of synapses changes across sleep depends on the brain area, on whether there was novel pre-sleep learning, and on the makeup and quality of the sleep¹⁴⁸. Many dendritic branches show a net loss of spines after sleep, with the remaining synapses being on average smaller^{149,150}. Along with that, synapses contain reduced amounts of GluA1, particularly phosphorylated GluA1, and GluN2A, without a reduction in GluA3 or GluN2B after sleep compared with wakefulness^{151,152}. These effects of sleep on synapses show an overall net decrease in LTP, and potentially a net increase in depotentiation, and are in line with the hypothesis that sleep promotes a global homeostatic downscaling of synapses after a wakeful period full of LTP-like activity^{10,153}.

Independent of the synaptic homeostasis hypothesis, our perspective is that the reactivation of memory traces during sleep induces synaptic plasticity at active synapses to benefit consolidation of systems (Fig. 4). In support of active sleep-dependent plasticity, spines that gain high levels of GluA1 after learning a new task also retain most of their GluA1 after sleep, indicating selective maintenance of the expression of LTP across sleep at these synapses¹⁵⁴. Furthermore, a population of cortical neurons that was active prior to sleep in fact selectively increase their activity during NREM sleep¹⁴⁵, which could promote the formation of distal dendritic spines¹⁵⁵. Moreover, during sleep spindles, neocortical neuronal activity increases and becomes synchronized with input to disinhibited distal dendrites^{144,156}, allowing large Ca²⁺ influx that could induce LTP (ref. 156). The concerted activation of subsets of synapses through replay of neuronal ensembles also probably triggers coincidence detection by NMDA receptors¹⁵⁷, which may also induce LTP – or at least prevent depotentiation. Indeed, studies characterizing dendritic spines of hippocampal pyramidal cells after sleep deprivation indicate that sleep normally prunes spines of proximal dendrites¹⁵⁸ while converting the distal dendritic boutons to shapes that are characteristic of late-phase LTP¹⁵⁹. Altogether, the

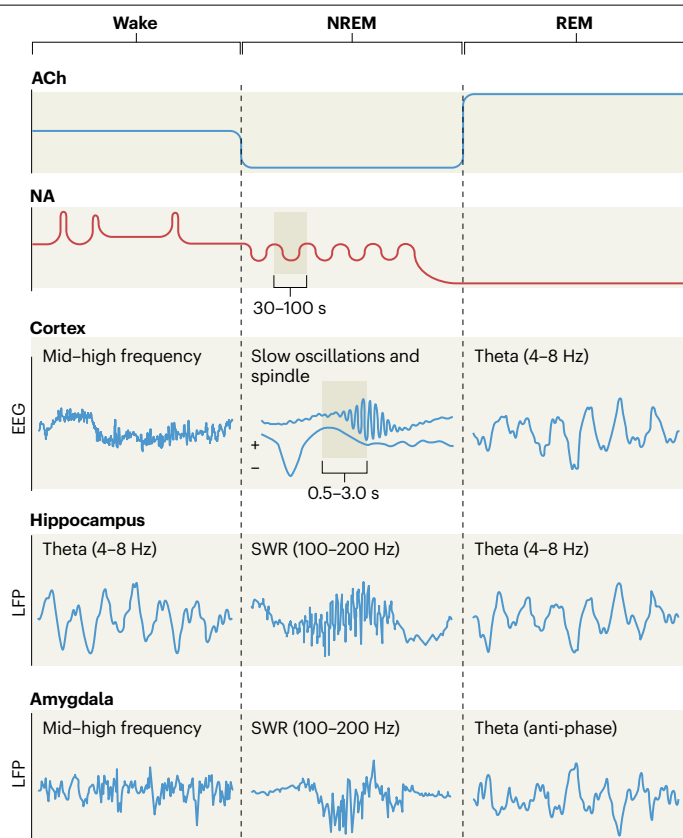


Fig. 4 | Neuromodulatory milieu and neurophysiology across wakefulness and sleep. The main source of noradrenaline (NA) is the locus coeruleus (LC). Its high tonic and phasic activity during wakefulness attenuates during NREM sleep and shows a cyclic pattern at infraslow timescales (30–100 s; red trace). This periodic LC activity leads to clustering of sleep spindles when NA levels are low. The absence of acetylcholine (ACh, top trace) during NREM sleep permits the generation of sharp wave–ripples (SWRs) in the hippocampus and amygdala. These SWRs can couple with thalamo-cortical spindles which in turn are coupled to cortical slow oscillations (EEG trace). During the transition from NREM to REM sleep, LC activity attenuates and is completely silenced during REM sleep, whereas cholinergic neurotransmission peaks. In this context, the cortex, hippocampus and amygdala exhibit theta-frequency oscillations. Theta oscillations can occur anti-phase in the amygdala relative to those in the hippocampus. These anti-phase oscillations may serve to disconnect the amygdala from the memory circuits, because activity at theta troughs has been shown to depotentiate synapses in the absence of NA. EEG, electroencephalography; LFP, local field potential; NREM, non-rapid eye movement.

selective maintenance of LTP can be linked with NREM sleep spindles to support the consolidation of novel memory traces into neocortical schemas¹⁶⁰.

In addition to sleep spindles, PGO waves, which appear during the transition to REM sleep in most cortical areas and the hippocampus, can deliver strong glutamatergic excitatory drive and evoke the intracellular events of LTP (ref. 161). These PGO waves are activated just after hippocampal sharp wave–ripples occur¹⁶² and target the pyramidal cells in the cortex and hippocampus in the same sleep state, the transition to REM sleep, when spindles induce a large Ca²⁺ influx to the distal

dendrites. Distal cortical dendrites are where cortico-cortical and higher-order thalamo-cortical communication occurs to support the maintenance of memory schema¹⁶³. Thus, NREM sleep may serve to (1) transfer memories that are reactivated in the hippocampus to the distal layers of the cortex through Ca^{2+} entry during spindles and through PGO waves and (2) strengthen the feedback signal to the CA1 familiarity pathway, indicating that such transfer has occurred.

NREM sleep is followed by REM sleep, which in turn supports further synaptic plasticity – albeit (1) with different neurophysiological field potentials, including theta oscillations, (2) with disproportional neuronal activity in the limbic circuits^{118–121} and (3) in a radically different neuromodulatory milieu, with low NA (refs. 14, 116, 117) and high acetylcholine levels^{121,122}. Through activation of both nicotinic and muscarinic types of cholinergic receptors, acetylcholine creates the conditions that can facilitate either LTP or LTD (ref. 164), depending on the timing of activity in relation to postsynaptic local membrane potential and theta phase^{165,166}. Cholinergic signalling promotes synaptic plasticity through mechanisms that are partly similar to NA signalling but also through divergent mechanisms¹⁶⁴, allowing for complementary cholinergic promotion of plasticity at both low levels of NA during REM sleep and high levels of NA during waking. Cholinergic signalling also induces the expression of Arc in active neurons¹⁶⁷, through which it could potentially promote synaptic weakening at inactive, novelty-encoding, proximal synapses during REM sleep. As we will discuss further in the next section, high acetylcholine levels during REM sleep support LTP at synapses that are coincidentally active during the replay of a memory trace, that is, at the distal dendrites that generate spikes in response to inputs arriving at the peaks of local theta oscillations. However, LTD or depotentiation is favoured when spikes arrive at local theta troughs, that is, when cholinergic activation of muscarinic receptors on interneurons locally inhibits postsynaptic depolarization^{168,169}. By promoting depotentiation, REM sleep – by means of the absence of NA – could provide the necessary conditions that favour the decoupling of the limbic synapses that represent the distressing part of an emotional memory trace. Indeed, Rexrode et al. have shown evidence that sleep downregulates spines in the central nucleus of the amygdala, which is responsible for governing autonomic and endocrine responses, whereas spines were strengthened in the basolateral amygdala, which has reciprocal connections with neocortical sensory and association areas including the medial prefrontal cortex (mPFC)¹⁷⁰. These findings align with the idea that sleep aids disengagement of the emotional response and strengthens top-down control from mPFC regions.

Abnormal noradrenaline levels during sleep. For sleep to provide the brain with periods of low NA, paraphrased as NA ‘time-outs’¹⁷¹, REM sleep should be consolidated. The decrease in downstream NA from the moment the LC is silenced is a slow process with a long time constant¹⁴. If this process is interrupted by an arousal, wakefulness or NREM sleep, and the LC resumes tonic activity, downstream NA shoots up with a short time constant. As a consequence, NA time-outs are unlikely to be reached in case of frequently interrupted ‘restless’ REM sleep, as has been observed in people with insomnia, depression, anxiety or post-traumatic stress disorder, as well as in a rat model of post-traumatic stress disorder (ref. 171). It has been proposed that a lack of NA time-outs is detrimental for synaptic plasticity processes that take place during REM sleep. Firstly, considering that NA and acetylcholine facilitate LTP via synergistic but distinct molecular mechanisms¹⁷², synapses that are active during memory replay may even come out to be stronger if NA levels are inappropriately high during REM sleep.

Furthermore, based on the evidence that NA has the capacity to inhibit LTD and depotentiation^{89–91}, a lack of NA time-out may prevent the necessary de-association of the emotional component of a memory. Indeed, Diering and colleagues have shown that mice had a stronger expression of a fear memory when sleep-specific downscaling of synapses was prevented after fear conditioning¹⁵².

The exact molecular mechanisms that separate those synapses that are targeted for sleep-induced downscaling from the ones that are spared or strengthened is yet to be determined, though it has long been hypothesized that PRPs, such as Arc, might be important for orchestrating this process. Recent reviews^{10,153} have proposed a model whereby the wake state is associated with learning and LTP, leading to the expression of Arc in memory engram neurons. The unique neuromodulatory milieu during sleep suppresses Arc expression in cortical neurons¹⁷³, but it may hypothetically be maintained in neurons that are reactivated during sleep, wherein Arc may serve to keep those memory traces intact. Thus, inappropriate NA signalling during sleep, through its effect on Arc expression, could interfere with the selection of which memories are either weakened or consolidated during sleep. Currently, there is little direct evidence to support this hypothesis, but it is an intriguing possibility that warrants further investigation.

Circuit-level plasticity during sleep

As discussed in the previous sections, distress adaptation can be related to hippocampal remapping of novel emotional memory traces onto the familiarity pathway and to depotentiation of amygdala–hippocampal connections. How can sleep contribute to these processes?

Remapping of novel memory traces onto the familiarity pathway.

Hippocampal remapping and its dependence on REM sleep theta oscillations were first shown by Poe and colleagues¹⁷⁴. After a session in which animals navigated first a familiar and then a novel track, the neural activity of the animals was monitored during sleep. Hippocampal CA1 neurons encoding novel environments fired primarily during REM sleep theta peaks, whereas the bursts of CA1 neurons encoding familiar environments occurred at theta troughs and selectively not at theta peaks. Importantly, the preferred firing phase of CA1 neurons during REM sleep shifted from theta peak firing on days 1 and 2, when the environment was still novel, to trough firing on days 5 and later. It follows that novel emotional memory traces can be initially maintained and even further potentiated during REM sleep, but once the memory is consolidated, the neurons encoding the now-familiar memories can depotentiate their novel synapses by firing at theta troughs.

What are the proposed mechanisms of this hippocampal remapping? During REM sleep, when NA is not present and cholinergic neuromodulation is high¹²², EC layer III is released from inhibition and becomes able to excite the distal CA1 inputs at local theta peaks. If those distal inputs have been potentiated by PGO waves and spindles during the prior NREM transition to REM sleep, then distal inputs during REM sleep have a greater tendency to generate dendritic spikes. The glutamatergic PGO waves that began in the transition to REM sleep occur with even greater density during REM sleep. These PGO waves arrive in synchrony with the distal dendritic theta peaks at hippocampal CA1 pyramidal cells in all animal studies: in cats, rats and monkeys^{135–137,175}. These distal dendrites are the destination of familiarity-encoding temporoammonic inputs coming from EC layer III neurons. During REM sleep, instead of being driven by hippocampal reactivation, PGO

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waves induce hippocampal CA1 cell reactivation during the distal theta peaks¹⁶². Furthermore, the absence of serotonin during REM sleep reduces the ionic leak conductance of the distal dendrites of CA1 neurons such that they more faithfully transmit distal inputs all the way to the cell body¹⁷⁶. Importantly, the phase of the theta oscillation in the LFP shifts -180° from the top to the base of the apical dendritic tree of the CA1 neuron¹⁷⁷. Therefore, the distal input that arrives at the local theta peak could support distal dendritic LTP and,

in the absence of serotonin, propagate the dendritic spikes to the soma past proximal dendrites, during a time when proximal inputs from CA3 are silent and their proximal theta phase is at its trough (Fig. 5b). This mismatch between postsynaptic depolarization and presynaptic silence would induce heterosynaptic depotentiation of those proximal novelty-encoding synapses according to the rules of spike timing-dependent plasticity¹⁷⁸, especially or solely in the absence of NA (refs. 89,91).

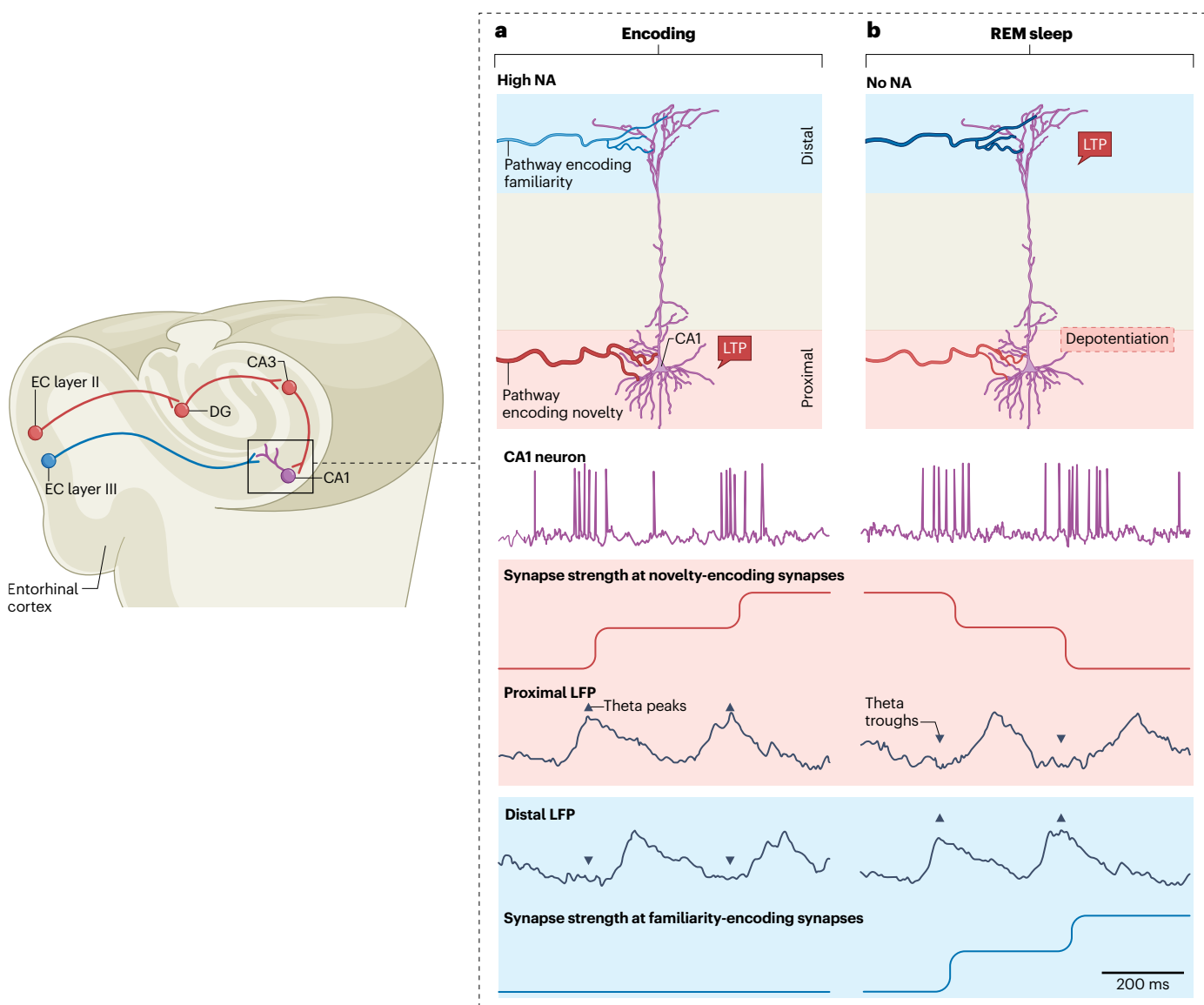


Fig. 5 | A proposed mechanism to remap a novel memory trace onto the familiarity-encoding pathway. The temporoammonic pathway between the entorhinal cortex (EC) and hippocampal CA1 subregion (blue) encodes familiarity, whereas the perforant pathway between the dentate gyrus (DG) and CA3 regions (red) encodes novelty. **a**, Noradrenaline (NA) inhibits the distal familiarity-encoding pathway (blue), whereas proximal CA1 novelty-encoding synapses (red) are activated at local theta oscillation-peak activity, which induces long-term potentiation (LTP). **b**, During REM sleep, when NA is absent, the CA1 neuron increases its sensitivity to distal inputs from EC layer III neurons, which

can induce LTP at the distal synapses of the CA1 neuron. Once distal connections are sufficiently potentiated, the CA1 neuron shifts its activity to proximal theta troughs. Now the novelty-encoding synapses can be depotentiated, as their input arrives at theta troughs. The phase of the theta oscillation also changes -180° along the axis of the CA1 neuron. Therefore, distal familiarity-encoding synapses are activated at local theta oscillation peaks, which induces LTP. Note that the presented traces are not actual data. LFP, local field potential; REM, rapid eye movement. Left image adapted with permission from ref. 244, Elsevier.

Indeed, this hippocampal function of remapping novelty-encoding memory traces onto the familiarity pathway seems to be critically dependent on the absence of NA during REM sleep. In a recent study, Grella et al. placed animals in a familiar environment while activating the LC or in a novel environment while blocking the LC (ref. 179). NA signalling to the hippocampus initiated the dentate gyrus to remap a familiar environment, that is, encoding it as a novel and salient environment. Conversely, blocking LC signalling in a novel environment resulted in activation of a familiar map. These findings show that novelty-encoding neuronal ensembles can be remapped onto familiarity-encoding ensembles when NA is absent. We can hypothesize that the absence of NA during REM sleep may be critical to promote activity in hippocampal familiarity-encoding pathways instead of novelty-encoding pathways in response to reactivation of emotional memory traces. By the same token, inappropriate NA signalling would promote the hippocampus to keep the emotional memory traces encoded in the novelty pathways³⁹. In this way, the emotional memory preoccupies the novelty-encoding pathways and remains current and salient.

A synergistic role for the microcircuitry between interneurons and pyramidal cells in the hippocampus favours activity in the familiarity-encoding pathway and inhibition of the novelty-encoding pathway during sleep¹⁴⁶. Similar microcircuitry in the neocortex may allow analogous schema building in the distal dendrites during NREM spindles and REM sleep and weakening of proximal dendrite ‘bottom-up’ inputs from, for example, thalamic inputs that were potentiated during waking sensorimotor experiences^{142–145} (Fig. 6a). Parvalbumin-expressing interneurons in both hippocampus and cortex predominantly inhibit pyramidal-cell somas. Parvalbumin interneurons are most active during REM sleep, thereby hyperpolarizing pyramidal cell somas^{142,143}. This means that proximal dendrite presynaptic input has a lower probability to lead to postsynaptic activity, which can induce heterosynaptic LTD and depotentiation in these proximal synapses. Synergistically, vasoactive intestinal peptide-expressing neurons are also most active during REM sleep, and they inhibit somatostatin-expressing interneurons such as oriens lacunosum moleculare neurons in the hippocampus or Martinotti cells in the cortex, which would otherwise inhibit the distal dendrites of pyramidal cells. Thus, the distal dendritic trees in the hippocampus and cortex are most strongly disinhibited during REM sleep^{142,143} at the same time as excitatory PGO waves are bursting at their peak activity in concert with distal dendrite theta peaks. PGO waves and disinhibited distal dendrites could induce dendritic spikes at the time when a REM-specific absence of serotonin permits those dendritic spikes to be conducted all the way to the axon hillock. Together, these mechanisms would promote LTD or depotentiation at the proximal novelty-encoding synapses (hippocampus) or thalamo-cortical inputs (cortex) and LTP at the distal familiarity-encoding synapses (hippocampus) and cortico-cortical connections (cortex). Over time in the hippocampus, once distal inputs have been potentiated sufficiently, the CA1 pyramidal neuron shifts to theta-trough dominated activity during REM sleep, which further promotes LTD at proximal novelty encoding synapses of the pyramidal neuron. This downscaling of the novelty-encoding synapses may be a mechanism for reduced prominence and normalization of emotional memories.

Depotentiation of amygdala–hippocampal connections. There is strong evidence for transient coupling between the hippocampus, amygdala and mPFC specifically during NREM sleep spindles^{36,180}, NREM sharp wave–ripples^{181,182} and REM sleep theta waves¹³⁴. CA1 axons

innervate both the amygdala and cortex¹⁸³. In the cortex, structural plasticity can happen during REM sleep, including both a high elimination rate of spines and strengthening of spines that were active in a pre-sleep learning task^{184,185}. This raises the question of whether this also applies to the amygdala, that is, whether the CA1 synaptic terminals in the amygdala are strengthened or eliminated.

Theta oscillation coherence between the amygdala and hippocampus and between the amygdala and mPFC during REM sleep predicts next-day fear expression during a fear memory recall test¹⁸⁶. More detailed mechanisms were shown by Lesting et al., who simultaneously measured local field potentials (LFPs) in the amygdala, hippocampal CA1 and mPFC in mice during extinction learning and next-day extinction recall^{138,139}. Theta oscillation coupling was not entrained to one particular brain region during fear expression in the initial trials of extinction learning, when the conditioned stimulus (CS+) still elicits distress as evident by freezing behaviour. Next-day recall of extinction memory elicited a different pattern. At times when the CS+ did elicit fear expression, theta oscillation coupling increased between the mPFC and hippocampal CA1 and between the mPFC and amygdala, but not between CA1 and the amygdala. At times when the CS+ did not elicit fear expression, theta oscillation coupling across CA1 and amygdala regions was phase-locked to that of the mPFC. This indicates that the extinction memory trace had changed across sleep in two ways: (1) a gain in control of the mPFC over activity in the hippocampus and amygdala and (2) a decoupling between the amygdala and hippocampus. Interestingly, the authors also experimentally modulated theta oscillation coupling between hippocampal CA1 and the amygdala during extinction learning, either in-phase or anti-phase. Whereas anti-phase coupling induced rapid extinction learning, in-phase coupling induced delayed fear extinction and increased next-day fear expression (distress).

Totty et al. have shown further evidence that the phase-angle of theta-oscillation synchronization between the amygdala and hippocampus during REM sleep after fear extinction predicts next-day fear expression¹⁴⁰. Animals that had in-phase theta oscillations between the hippocampus and amygdala showed increased freezing behaviour at the fear extinction recall test, whereas those with anti-phase coupling showed decreased freezing. This suggests that anti-phase theta synchrony between the hippocampus and amygdala promotes LTD and depotentiation of the CA1–amygdala pathway, whereas in-phase synchrony promotes LTP. We propose that if, and only if, the familiarity pathway is sufficiently potentiated, the CA1 neuron switches its activity -180° to firing at distal theta peaks, and the theta synchrony between the distal CA1 region and the amygdala switches to anti-phase synchrony. As a result, CA1 input back to the amygdala now arrives at local theta troughs, which is linked to LTD and depotentiation of the CA1–amygdalar synapses (Fig. 6b). In short, this constitutes a negative feedback loop whereby emotional memories are preferentially consolidated, but that this consolidation process also leads to the downscaled connections with the amygdala stress output region of the central nucleus, allowing adaptation of memories associated with distress. Conversely, continued theta oscillation peak firing in the presence of LTP-promoting NA may instead even lead to further potentiation of novelty-encoding pathways, possibly leading to a worsened emotional response after sleep, rendering sleep maladaptive. This hypothesis is in line with the model of Vanderheyden et al. wherein saturation of novelty-encoding pathways could also prohibit the encoding of subsequent fear-extinction memories, preventing the adaptation of fear expression³⁹. Together, these mechanisms may also explain why

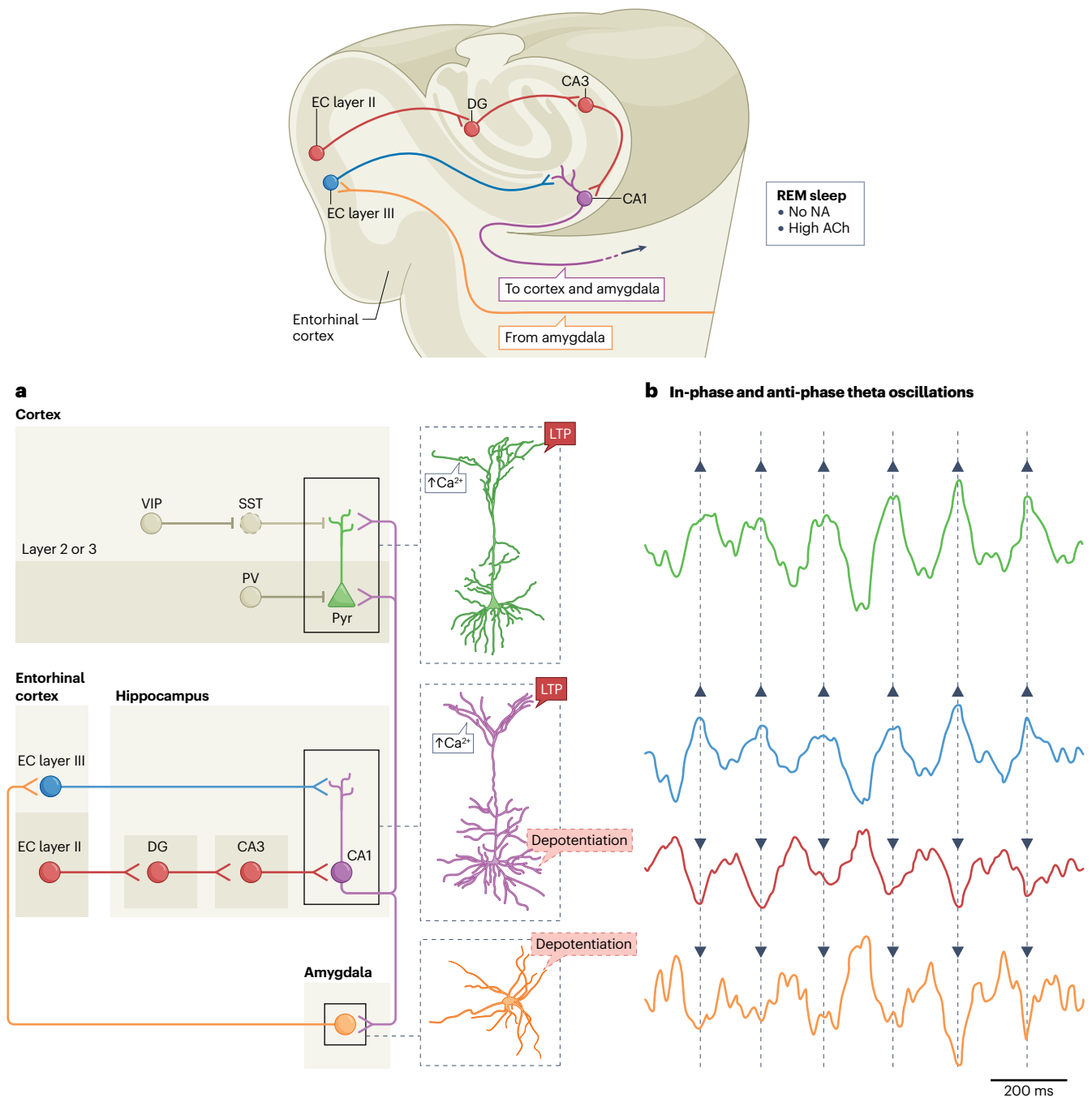


Fig. 6 | Depotentiation of amygdala–hippocampal connections through in-phase and anti-phase theta frequency coupling during REM sleep. Inputs to the entorhinal cortex (EC) from the amygdala predominantly arrive at the familiarity-encoding EC layer III. In turn, the CA1 region projects to the cortex and back to the amygdala. **a**, Memory reactivations during REM sleep activate EC layer III neurons, the distal dendrites of the CA1 pyramidal neuron, and cortical targets. In both the CA1 region and the cortex, the cell somas are hyperpolarized by PV interneuron activity and the pyramidal dendritic tree is most strongly disinhibited through VIP-interneuron inhibition of SST interneurons. This leads

to dendritic calcium (Ca²⁺) influx and can promote local long-term potentiation (LTP). **b**, Under strong cholinergic modulation during REM sleep, the cortex, hippocampus and amygdala exhibit theta oscillations. The theta synchrony between the distal CA1 region and the amygdala can switch to anti-phase synchrony (blue and orange traces), which can depotentiate the CA1–amygdala synapses. Note that the presented traces are not actual data. ACh, acetylcholine; DG, dentate gyrus; NA, noradrenaline; PV, parvalbumin; Pyr, pyramidal neuron; REM, rapid eye movement; SST, somatostatin; VIP, vasoactive intestinal peptide. Top image adapted with permission from ref. 244 Elsevier.

deprivation or inhibition of restless, maladaptive REM sleep has therapeutic effects in depression – it may be better to have no REM sleep at all instead of restless REM sleep.

Sleep and emotional memory in human studies

Although molecular and animal studies provide the basis for our thesis that overnight adaptation of distress depends on sound sleep, the main limitation of these studies is that they are not performed in humans. Therefore, we next discuss how the evidence is further corroborated by human studies using neuroimaging and autonomic markers of emotional distress.

Neuroimaging and autonomic markers of overnight adaptation.

As discussed in the previous sections, a novel emotional experience is encoded as synchronized neuronal activity across various sensory, motor and association cortices, as well as the limbic and salience circuit, and the noradrenergic central arousal system seeded by the LC in the brainstem^{2,3}. This pattern of activity is changed upon recall or cued re-exposure following sleep-dependent system consolidation. The memory trace becomes less dependent on hippocampal activity and instead becomes more dependent on functional coupling of cortical networks^{23,24,187,188}. Subsequently, these cortical branches of the memory trace, for example, in the infralimbic area of the mPFC, are proposed to inhibit the activity of the limbic representations in the amygdala^{24,188–190}. Indeed, the amygdala shows attenuated reactivity to cued recall of emotional memory following sleep^{17,189,191} and increased reactivity following sleep deprivation¹⁸⁸. Furthermore, after sleep, the mPFC shows increased functional connectivity with the hippocampus¹⁸⁸ and amygdala^{189,192}. This gain of control of the mPFC over the limbic regions is lost after sleep loss^{193,194}, which correlates with self-reported anxiety¹⁹⁰. Whereas cortical consolidation seems to depend mostly on NREM sleep, limbic depotentiation probably depends more on REM sleep. However, we hypothesize that the two sleep states interact to sort consolidation and depotentiation, because the effect of REM sleep on the adaptation of the amygdala becomes stronger in proportion to the abundance of sleep spindles in the transition to REM sleep¹⁷. This finding suggests that the adaptation of amygdala reactivity requires consolidated REM sleep, but said adaptation may also require priming by memory trace reactivation during the preceding NREM period.

Next to amygdala reactivity, objective markers of distress can be found in autonomic responses including transient heart-rate deceleration, reduced heart-rate variability and galvanic skin-conductance responses. Three studies have reported either no significant changes in autonomic markers⁴ or even increased skin-conductance responses^{195,196} across sleep. By contrast, six studies have shown that some autonomic measures adapted across sleep and did not change or even worsened across wakefulness^{5,6,197–200}. Adaptation differences across wake and sleep are not necessarily uniform across autonomic responses in heart-rate parameters and skin conductance^{6,199,200}. Adaptation differences could also take time to appear, for example, they could become visible after 1 week but not yet be present after 10 h (ref. 5). Together, these studies suggest that distress adaptation across sleep can differ depending on the type of autonomic marker, the duration of the interval and the intensity of the emotional stimulus. It has been proposed that distress may initially maintain or worsen across a single sleep period with REM sleep but adapts over the longer term with multiple ‘rounds’ of REM sleep processing²⁰¹.

The difference in distress adaptation across the first sleep period following the initial exposure compared to later sleep periods may be

related to changes in sleep elicited by the pre-sleep distress. Pesonen et al. have studied naturally occurring and normative cortisol levels prior to sleep in healthy adolescents²⁰². They showed that those with higher pre-sleep cortisol levels have less fragmented REM sleep. Secondly, among adults exposed to fear conditioning prior to sleep, those with a more reactive mPFC showed a stronger increase in REM sleep duration and decrease in fear²⁰³. Finally, exogenous boosting of cortisol after an emotional task enhanced the overnight adaptation of amygdala reactivity to re-exposure of emotional stimuli²⁰⁴. These studies show that within normative levels, pre-sleep arousal may evoke a type of resilient sleep characterized by increased REM sleep and overnight adaptation. Conversely, exceedingly strong or chronic pre-sleep emotional distress may evoke restless sleep characterized by arousals²⁰⁵, which resembles the sleep that is typical of anxiety-related, mood-related and stress-related disorders^{206–208}. Arousals and other indicators of restless REM sleep are associated with difficulties in emotion regulation²⁰⁹ and hamper overnight adaptation of amygdala reactivity and galvanic skin-conductance responses when re-exposed to emotional stimuli^{17,189,210}. We propose that these effects of stress on sleep are key to the mechanisms involved in interference with distress adaptation.

A study applying targeted memory reactivation (TMR) during sleep has provided the most direct support for a key role of sound versus restless REM sleep in determining subsequent adaptation versus sensitization or amygdala reactivity¹⁷. After conditioning an odour to a distressing stimulus in the evening, subsequent exposure to the odour during sound REM sleep facilitated overnight adaptation of amygdala reactivity during re-exposure of the distress. By contrast, TMR during restless REM sleep impeded overnight adaptation. Similarly, Bottary et al. investigated overnight changes in skin-conductance responses following extinction learning²¹¹. Among participants without sleep complaints, individuals who spent more time in REM sleep had the greatest reduction in skin-conductance responses. Remarkably, participants with insomnia who spent more time in REM sleep showed increased skin-conductance responses. Attenuated fear extinction and adaptation of limbic and salience networks in insomnia have also been shown by others²¹². Of note, insomnia is a condition characterized both by a stronger sleep-disruptive effect of daytime distress and by marked fragmentation of sleep, and in particular REM sleep²⁰⁶. Overnight adaptation to emotional distress may, thus, depend on the extent to which the pre-sleep experience resonates to induce resilient or restless sleep, determining whether distress ameliorates, does not change or worsens across the night.

Taking this observation to a long-term perspective may help to clarify the development of chronic restless sleep and pervasive emotional distress. Early-life trauma was observed to result in more restless REM sleep in adulthood²¹³. Moreover, the risk of developing post-traumatic stress disorder increases with restlessness of REM sleep, reduced REM sleep theta power and higher metabolic rates during REM sleep in brain regions involved in arousal, fear and reward processing^{207,214–216}. Patients with insomnia patients show stronger reactivity of the dorsal ACC and stronger autonomic nervous system responses while recalling remote emotional memories of even decades ago⁶⁰. The functional connectivity of the dorsal ACC with the LC is also altered in insomnia, and individual differences in connectivity strength are associated with the severity of experienced anxiety²¹⁷. In summary, aberrant functional coupling between ACC and LC may reflect chronic inefficiency of overnight dissolving of emotional distress and the risk of developing mental health problems.

Subjective arousal ratings. Next to the objective assessments, emotional distress can also be probed using subjective distress ratings. Several studies addressed whether sleep can facilitate adaptation of subjective distress overnight. These studies have varying designs and mixed results.

First, discussing studies of overnight distress adaptation across wake, sleep and sleep deprivation, a slight majority of studies suggest that sleep following emotional experiences facilitates adaptation of self-reported distress or arousal^{196,218,219}, more than wakefulness does^{189,220–222}. One study reported stronger adaptation across wakefulness than across sleep²²³. Other studies report adaptation of self-rated arousal irrespective of whether participants slept or stayed awake^{5,198–200}. Finally, some studies failed to observe any change in self-rated arousal to negative or neutral stimuli across intervals of sleep, natural wakefulness or sleep deprivation^{4,224–227}. Differences in study design and presentation of stimuli may explain the variability in findings. Eight out of the ten studies that found either no change in distress or no difference between sleep and wakefulness included novel negative stimuli during the second exposure (post-sleep or post-wake)^{4,5,199,200,223–225,227}. By contrast, among the seven studies that did find stronger adaptation to distress across sleep than across wakefulness, only one study presented novel emotional stimuli at the second exposure²¹⁹. It is conceivable that the studies that found a lack of (differential) changes in emotional distress across sleep may have used a suboptimal experimental design by introducing novel emotional stimuli during the second exposure. It has been argued that these novel stimuli are necessary to distinguish between memory-specific processes and general changes in emotional reactivity²²⁸. However, this argument assumes that the emotional distress induced by a single negative stimulus, for example, an image, is unique to the memory of that single image and independent of induced distress from other stimuli within the context of the experiment. We do not think this assumption holds, because regulation of emotional reactivity does depend on the context²²⁹. Furthermore, if the function of sleep was to reduce general emotional reactivity, then emotional reactivity ratings at the first exposure in mornings should be lower than in evenings, but none of the aforementioned studies report such a difference. In conclusion, the subset of studies that did not show novel emotional stimuli at the second exposure mostly indicate a facilitating role for sleep in overnight subjective distress adaptation.

Secondly, several studies addressed the question of whether adaptation of subjective emotional distress depends more on NREM or REM sleep. Whereas one study reported overnight adaptation of self-rated arousal irrespective of whether participants were deprived of NREM or REM sleep²³⁰, other studies have reported no significant changes across 3-h intervals over early-night versus late-night sleep²³¹ or across sleep that included both NREM and REM sleep²³². Of note, a study on overnight sleep reported adaptation in the group that was selectively deprived of REM sleep. This was contrary to three other studies reporting that REM-sleep deprivation led to a lack of adaptation^{201,233} or even a worsening of emotional distress²³⁴. Finally, compared with experimental deprivation of specific sleep stages, sleep that includes both NREM and REM sleep has been shown to support distress adaptation²³³, at least in the long term²⁰¹. In summary, with the exception of the study by Lara-Carrasco and colleagues²³², these findings are in line with the proposed integrated role of multiple NREM–REM sleep cycles in overnight consolidation of emotional memories and adaptation to their distress^{17,235,236}.

Targeted memory reactivation. Enhanced adaptation in subjective arousal across sleep has been shown in studies applying TMR during REM (refs. 237,238) and during stage 2 NREM sleep^{237,239,240}. Another study concluded that TMR during slow-wave sleep did not influence overnight changes in arousal ratings²⁴¹. Next to subjective ratings, three studies did not find that TMR during sleep further enhanced overnight adaptation in skin-conductance responses^{210,237,242}; however, the number of stimulations during REM sleep and REM sleep duration did correlate with adaptation of autonomic responses²⁴². Furthermore, two studies applying TMR during REM sleep found effects on overnight adaptation of amygdala reactivity^{17,241}, and one study applying TMR during NREM sleep showed enhanced adaptation in the hippocampus and amygdala²⁴³. In conclusion, although not unequivocally, studies using TMR have shown more direct support for a role of sleep in overnight adaptation of distress.

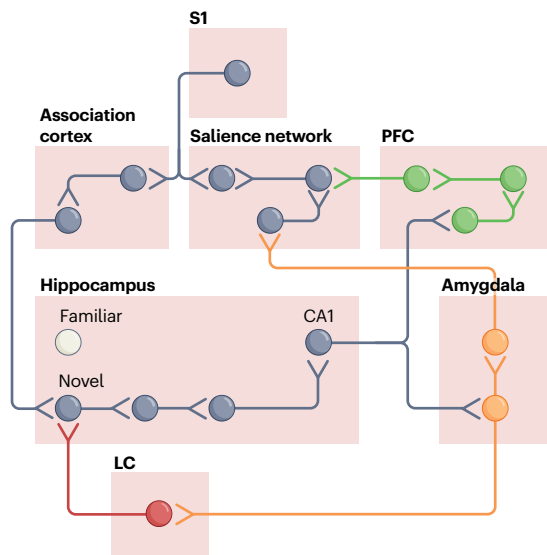
Conclusion, critical evaluation and summary

The presented model generates testable hypotheses regarding the factors involved in sleep-dependent consolidation of emotional memory and distress adaptation, and how failure of this process owing to continued LC activity during sleep (and REM sleep in particular) may be key to the development and maintenance of mental disorders. On the one hand, the model is built on well-known observations across molecular and cellular, neuronal circuit, brain system and behavioural levels that show how reactivation of engram neurons during sleep induces overnight plasticity related to memory consolidation in cortical schemas, gradual adaptation of limbic representations, and dissipation of autonomic distress. On the other hand, the model is built on recent and scarce observations that require further replication and mechanistic understanding. This is specifically true for the mechanisms underlying (1) synapse-specific localized translation of PRPs during sleep and their role in synaptic tagging during sleep-dependent memory consolidation, (2) strengthening and weakening of distal and proximal synapses, respectively, to support hippocampal remapping and cortical schema formation, and (3) how overnight memory consolidation and dissipation of distress critically depend on activity or inactivity of interneuron types and neuromodulators during specific sleep stages and their neurophysiology (for example, arousals, NREM slow oscillations, spindles and REM theta rhythms). Moreover, we note that the strongest support for a role of consolidated REM sleep in overnight distress adaptation is provided by a handful of studies on self-conscious emotions, which are clinically most relevant for mental health (for example, self-conscious shame and guilt, self-worth, hopelessness and bereavement). A larger number of studies on overnight distress adaptation used emotional images without self-relevance, which may be of secondary importance for mental health. The further development and use of self-conscious emotion paradigms in both resilient and vulnerable populations are recommended.

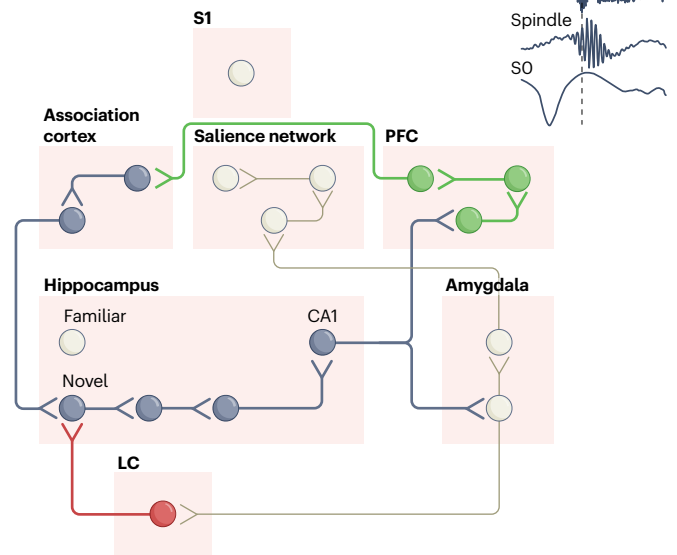
In summary, later recall of emotional memories normally occurs with reduced subjective distress, decreased autonomic nervous system responses, and reduced activity in limbic and salience circuits of the brain (Fig. 7). Sleep is a critical time during which specific brain states can (1) selectively consolidate and integrate the facts and cognitive components of a memory and (2) disengage the emotional or limbic circuit and novelty or salience network and gain control over the fight–flight–freeze autonomic nervous system. First, NREM sleep is a time window of low cholinergic modulation, which permits the generation of sharp wave–ripples that couple with thalamo-cortical spindles and cortical slow oscillations. This coupled synchronous activity

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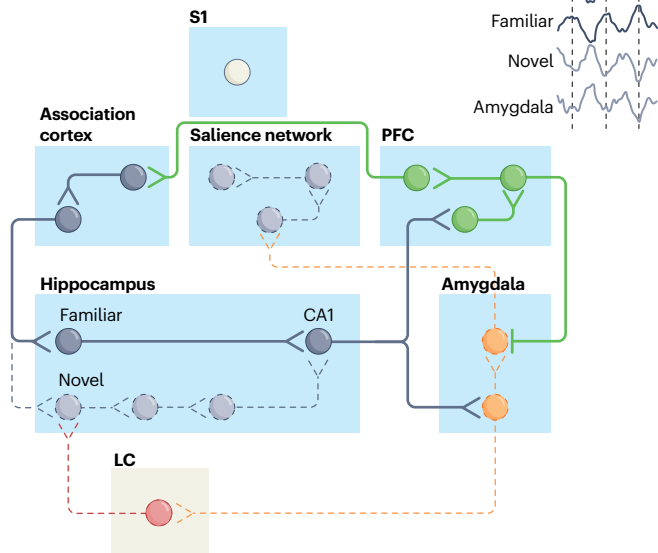
a Wake (novel distressing experience)



b NREM sleep



c REM sleep



d Wake (recall)

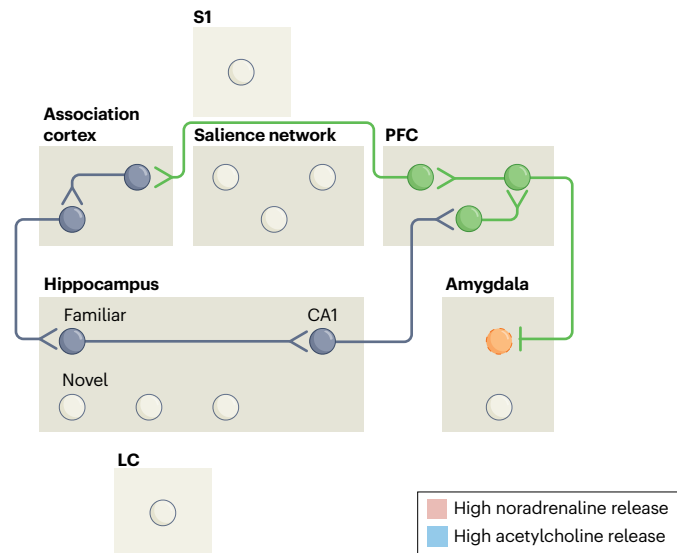


Fig. 7 | Proposed model of memory consolidation and distress adaptation across sleep. Dark grey and light grey circles indicate active and inactive engram neurons, respectively. Solid and dotted lines indicate long-term potentiation (LTP) and depotentiation, respectively. **a**, Distressing experiences activate the locus coeruleus (LC), which releases noradrenaline (NA; red boxes) and promotes memory encoding across brain networks including the somatosensory (S1) and association cortices, the salience network, limbic system (hippocampus and amygdala), and prefrontal cortex (PFC). NA biases memory encoding in the hippocampal novelty pathway. **b**, Memory reactivation during NREM sleep is linked with neurophysiological coupling of sharp wave–ripples, spindles and slow oscillations (SO, insert). This coupling occurs when tonic LC activity is low, but phasic LC activity has been observed during spindles and SO (light red boxes). The synchronous neuronal activity and modulation by NA may

promote LTP at the disinhibited distal dendrites, which is proposed to support the formation of cortical memory schemas (for example, between PFC and association cortices). **c**, REM sleep is a time of low NA (inactive LC) and high cholinergic modulation (blue boxes), which permits theta-oscillation coupling between limbic regions and the PFC (insert shows dark in-phase and light anti-phase traces). Anti-phase coupling is proposed to depotentiate connections in the novelty pathway and the amygdala and salience network. In-phase activity may promote LTP in the familiarity pathway and PFC and a gain in control over the amygdala (inhibitory connection). **d**, Next-day recall activates engram neurons that have undergone or maintained LTP across cortical regions, and the hippocampal familiarity pathway, but no longer activates the salience network, amygdala or LC, as these connections have been depotentiated (white circles) or are inhibited (for example, in the amygdala).

reactivates – in fast forward – the sequence of activity as it occurred during the waking learning experience. Furthermore, this coupled activity between the hippocampus and cortical systems during sleep spindles can specifically strengthen the memory trace in the distal dendrites of the neocortex, wherein memory schemas are formed and updated. The transition from NREM stage 2 to REM sleep also features PGO waves that selectively strengthen the distal dendrites carrying the familiarity trace back to CA1 hippocampal cells. Second, REM sleep is a unique time window of high cholinergic and virtually absent NA modulation, which permits theta-oscillation coupling between limbic regions and the cortex. The absence of NA has been shown to induce hippocampal remapping: the re-encoding of the memory trace from novelty-encoding pathways to familiarity-encoding pathways. Once the familiarity-encoding synapses are potentiated, the hippocampal CA1 neurons shift their activity from theta oscillation peaks to troughs, which has been shown to promote depotentiation of novelty-encoding synapses, readying the learning system for a new day of associative learning. The change in timing of neuronal activity from in-phase to anti-phase theta oscillations is also relevant for ‘uncoupling’ the memory trace connections with the amygdala. Memory trace reactivations during REM sleep can occur during the troughs of theta oscillations in the local field potentials of the amygdala, which might, like in the hippocampus, permit LTD or depotentiation. These overnight plasticity processes during sleep should also result in changes in the structure (enlargement, pruning) and function (addition or removal of receptors) of individual synapses. Indeed, recent studies show highly selective potentiation and pruning of individual synapses during REM sleep.

However, the precise balance between LTP and LTD during REM sleep can be grossly disturbed by inappropriate NA signalling. NA both prevents LTD and promotes LTP by enhancing the likelihood of NMDA-receptor-mediated coincidence detection, increasing the Ca²⁺ conductance of NMDA receptors, and inserting AMPA receptors into synapses. NA can also mediate the induction of late-phase LTP, which can solidify synapses to be robust against later depotentiation. At the level of neuronal circuits, anti-phase theta oscillations between the distal CA1 region and amygdala normally permit LTD. However, the amplitude of these oscillations can be reduced by continued NA signalling. This may, in combination with the NA blockage of depotentiation, prevent depotentiation of connections between the amygdala and hippocampus. Secondly, continued NA signalling during REM sleep would prevent the hippocampus from remapping novel and salient information into familiarity-encoding pathways. Whereas normally the activity from familiarity-encoding pathways facilitates the depotentiation of novelty-encoding pathways, in the presence of NA, this depotentiation does not occur. In fact, we propose that continued NA signalling during REM sleep could even further potentiate and saturate the novelty-encoding pathways, which prohibits the encoding of subsequent adaptive fear-extinction memories. This could mean that no REM sleep at all may be better than restless REM sleep, and it could explain the therapeutic effects of REM sleep-reducing antidepressants. Patients with insomnia have more restless REM sleep compared with normal sleepers, have impaired overnight adaptation to emotional distress, and are at risk of mental health problems. Although our focus was on insomnia, the maladaptive sleep may well be applicable to other sleep disorders such as sleep apnoea.

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