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Stress, sleep, and the selective consolidation of emotional memories

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Memory consolidation processes can be highly selective. For example, emotional aspects of events tend to be consolidated more readily than other, more neutral aspects. We first describe evidence that the sleeping brain provides an ideal environment for memory consolidation, and that active, as opposed to passive, sleep-based consolidation processes are particularly important in explaining why emotional memories are retained so well. We then briefly review evidence that elevated levels of stress support emotional memory consolidation. Finally, we propose a working model that describes why stress at encoding may set the stage for sleep to etch emotional memories in the brain on a lasting, if not permanent, basis, and we present recent data to support this model.

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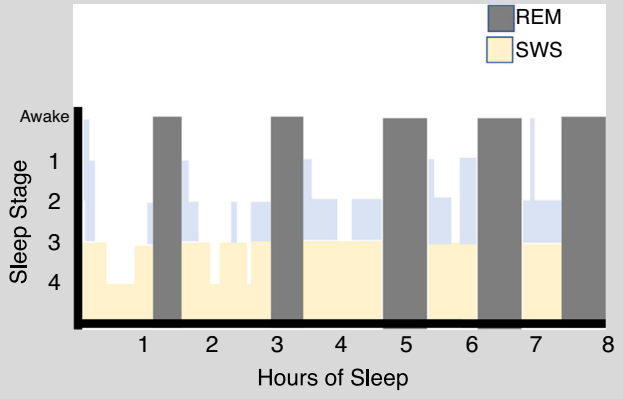
Memory for negative events is a double-edged sword. Although our ability to learn from and remember negative experiences is critical for survival, negative memory biases contribute to the etiology and perpetuation of affective disorders [1–3]. Recent research emphasizes that to understand how memories for negative events become etched in the brain, it is necessary to consider both the stress and arousal experienced during the event and the sleep that occurs shortly thereafter.

Although it is well known that emotional memory formation can be enhanced by sleep (e.g. [4,5]) and by stress exposure (e.g. [6–8]), only recently has research investigated how sleep and stress *interact* to influence emotional memory consolidation. Yet there is biological and psychological evidence for an overlap between these factors. For example, the stress hormone cortisol peaks during late-night rapid eye movement (REM)-rich sleep, and elevated stress is a common trigger for sleep disruption (and vice versa; [9]). Recent evidence from our laboratories suggests that the sleeping brain's ability to selectively enhance emotional memory consolidation depends on stress and arousal levels *at the time of learning*, with stress responses during learning setting in motion a cascade of neurochemical events that lead to downstream selective consolidation of emotional aspects of memories. These results link the traditionally separate fields of stress and sleep by making two complementary suggestions: first, elevated stress and arousal responses during learning maximize downstream sleep-dependent emotional memory consolidation effects, and second, sleep in the delay interval enables stress-based emotional memory consolidation effects to emerge. We begin with brief reviews of the literatures that separately link sleep and stress to the consolidation of emotional memory and then return to the idea that stress during learning interacts with subsequent sleep to optimize the consolidation of emotional memories.

Sleep and emotional memory consolidation

Consolidation processes, which occur slowly following learning [10], depend on a molecular cascade leading to structural and functional changes in neurons [11]. Multiple levels of analysis suggest that the offline brain state of sleep provides ideal conditions for consolidation [12,13], including emotional memory consolidation ([14,15]; see Box 1). At the molecular level, there are several immediate early genes related to synaptic plasticity (e.g. *zif-268*) that are up-regulated during REM sleep in response to manipulations and memory tasks targeting the amygdala and hippocampus (HC) [16–18], suggesting that sleep constitutes a privileged window for consolidation of emotional memories within larger associative networks [19–21]. At the cellular and regional levels, activation patterns seen during daytime task training in the rat (e.g. [22]) and human HC [23,24] are reactivated during subsequent slow wave sleep (SWS). Moreover, medial temporal regions, including the amygdala and HC, are more active during REM sleep than during wakefulness [25,26]. Thus, although sleep is a state of behavioral quiescence, it is associated with intense neuronal activity, increased expression of key plasticity-related genes in the brain, reactivation of neuronal assemblies involved in learning, and functional increases in brain areas

Box 1 Sleep stages and emotional memory consolidation.



Sleep is not uniform across the night. The two stages of sleep most closely linked to selective memory consolidation are REM and SWS.

REM:

- The amount of REM sleep obtained often correlates with improved memory for emotional information (e.g. [31–36]) and to neural activity during retrieval of emotional information [37], including neutral information previously studied in an emotional context [38].

SWS:

- SWS during a nap relates to selective consolidation of emotional information [39].
- During overnight sleep, slow oscillatory activity links to memory for content with future relevance [40], and NE blockade during SWS disrupts temporal memory for emotional information [41].
- For memories cued during sleep, SWS duration and SWS spindles relate to facilitated memory judgments for emotional information [42].

Interactions between SWS and REM:

- Sequential models of consolidation, whereby SWS enables network-level reconfiguration of memory traces, and REM sleep operates upon those reconfigured traces (e.g. [43–45]) may apply to emotional memory [46].

necessary for emotional memory processing. Moreover, sleep often selectively benefits the consolidation of emotional over neutral information [14] and leads to strengthened connectivity within an emotional memory retrieval network [27•,28–30]. These lines of evidence provide compelling support for an active role for sleep in memory processing, as opposed to merely a passive role involving circadian influences or protection for waking interference [4].

Stress hormones and emotional memory consolidation

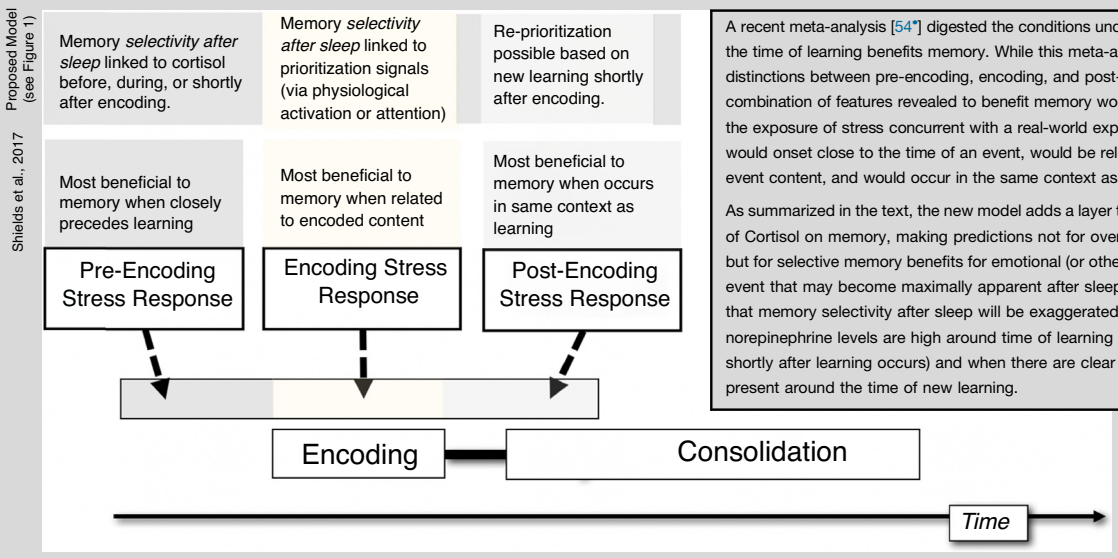
Like sleep, stress exposure often benefits memory consolidation, particularly for emotionally arousing experiences [47]. The sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis work in concert to enhance memory for emotional information during times of stress [8], likely because concurrent cortisol and norepinephrine activity in the basolateral amygdala intensifies interactions among the amygdala, HC and other memory-relevant regions such as the vmPFC. Given the importance of this network for emotional memory, its potentiation by stress is thought to underlie behavioral evidence for selective consolidation of emotional memories over neutral ones. In humans, stress exposure facilitates the consolidation of emotionally arousing, relative to neutral, pictures and stories [48,49], and even enhances emotional relative to neutral features within a single complex episode [7]. Evidence from multiple levels of analysis, from cellular analysis to fMRI studies, have demonstrated that while elevated stress often impairs HC and PFC function, amygdala function is enhanced (e.g. [50,51]). In humans, the cortisol response associated with stress exposure correlates with HC deactivation [52], with enhanced amygdala activity, and with better subsequent memory for emotional information [53]. Each of these lines of work highlights the importance of stress and cortisol during learning on the downstream consolidation of memory for emotionally arousing experiences.

Stress can enhance emotional memory consolidation regardless of whether exposure directly precedes, directly follows, or occurs during new learning. While a new meta-analysis ([54•]; see Box 2) suggests that the effects of pre-encoding stress on memory are varied, sleep has rarely been considered as a mediating factor. Yet nearly all studies showing a beneficial impact of stress on emotional memory examine memory after delays of 24 hours or more, necessitating a period of sleep in the retention interval [38]. Indeed, in most studies showing emotional memory enhancement by stress, sleep has occurred shortly after the new materials are learned.

Working model: stress near new learning interacts with sleep to enable selective emotional memory consolidation

As reviewed above, sleep and stress have separately been tied to enhanced emotional memory consolidation. Distinct from this is the idea that factors operating *near new learning* (e.g. just before, just after, or during the learning event) set the stage for downstream selectivity in sleep-based memory consolidation, which in turn leads to the persistence of emotional aspects of memories [55]. Here, we propose a model that makes two novel predictions about how these interactions between learning and consolidation occur. First, arousal-related neuromodulators (e.g. norepinephrine, cortisol) present during and after learning help set molecular 'tags' that designate specific traces of emotional (or other salient) information within an event to be prioritized for consolidation. Importantly, the very concept of a 'tag' seeks to explain how neural

Box 2 Encoding-related stress and selective memory consolidation.

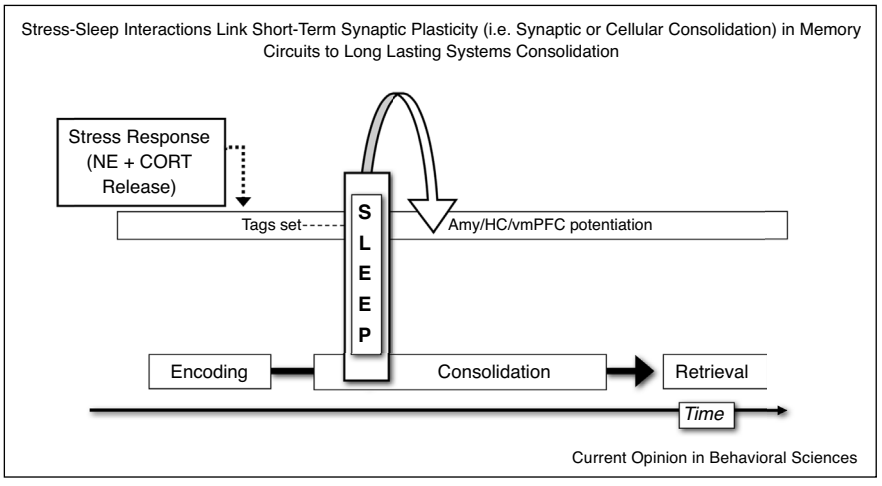


A recent meta-analysis [54•] digested the conditions under which stress around the time of learning benefits memory. While this meta-analysis emphasized distinctions between pre-encoding, encoding, and post-encoding stress, the combination of features revealed to benefit memory would be consistent with the exposure of stress concurrent with a real-world experience: The stress would onset close to the time of an event, would be relevant to the encoded event content, and would occur in the same context as the encoded event.

As summarized in the text, the new model adds a layer to the proposed effects of Cortisol on memory, making predictions not for overall effects on memory but for selective memory benefits for emotional (or other salient) aspects of an event that may become maximally apparent after sleep. The model proposes that memory selectivity after sleep will be exaggerated when Cortisol and norepinephrine levels are high around time of learning (before, during, or shortly after learning occurs) and when there are clear prioritization signals present around the time of new learning.

signaling creates a target for subsequent plasticity-related products (PRP) that are essential for sustained and *selective* plasticity in neural circuits. Thus, such tags, which are set during or near the learning event [56,57•], ensure memory specificity by guaranteeing that PRPs required for memory stabilization are captured only by activated representations and not others, thereby setting the stage for consolidation of selective event features to occur. This stabilization process enables the relevant representations to retain their strength for at least several hours. Although we cannot measure these tags directly in humans, we propose that evidence of these tags exists in strengthened connectivity among regions critical for emotional memory — the amygdala, hippocampus, and ventromedial PFC — as well as in improved behavioral performance (i.e. behavioral tagging [58••]) for emotional relative to neutral content. Second, and critically, the model argues that the unique high frequency stimulation and

Figure 1

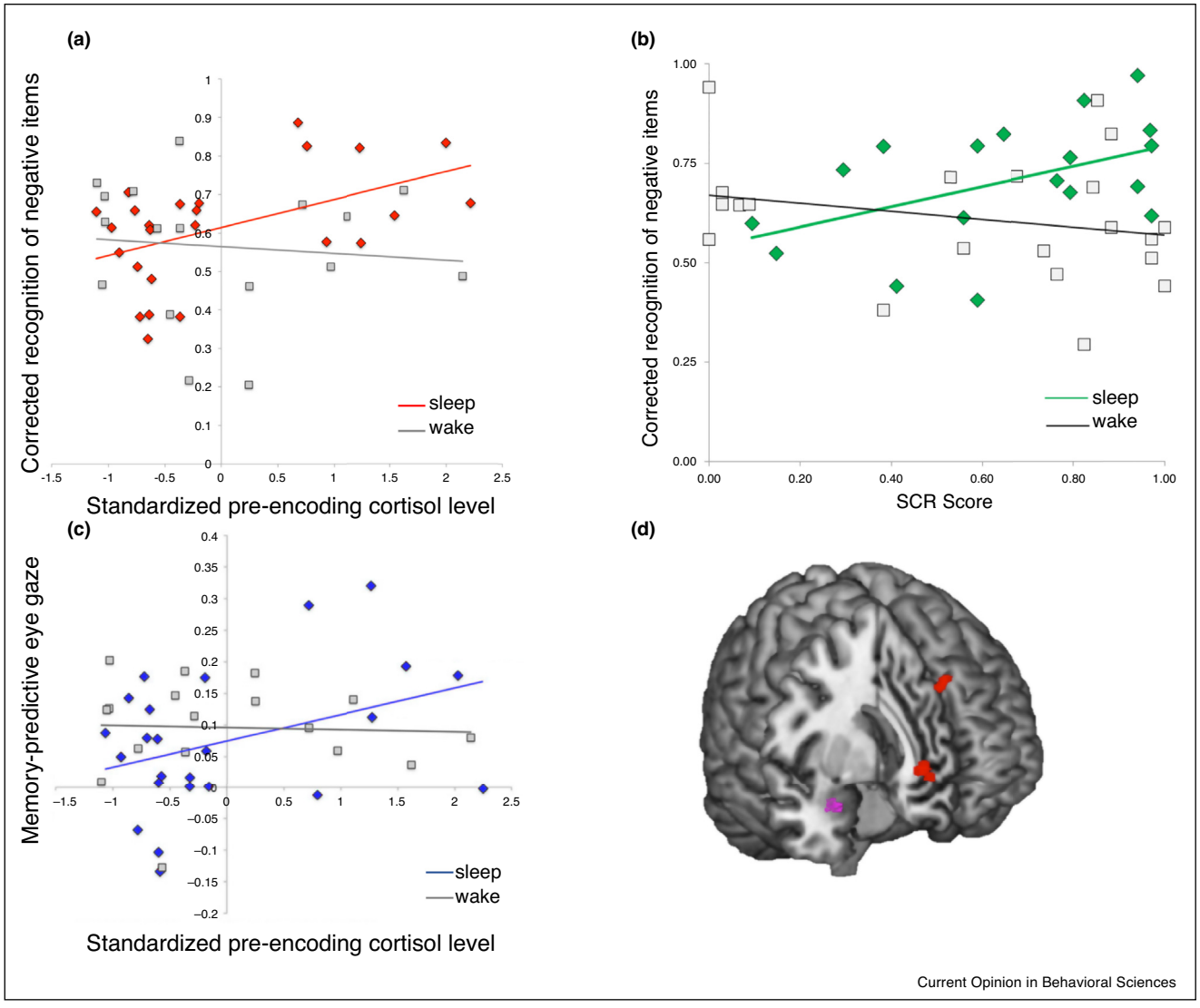


During an emotional experience, stress-related and arousal-related neuromodulators are released. Their presence helps set molecular tags that mark key features of an emotional experience. The unique, high-frequency stimulation that occurs during post-learning sleep (e.g. hippocampal sharp wave ripples, sleep spindles, theta rhythm) further potentiates these changes, helping to translate shorter-term synaptic changes into the long-lasting changes that underlie systems consolidation.

reactivation that occurs during post-learning sleep is essential for linking these distributed tags into the integrated memory trace that allows long-lasting systems consolidation. In other words, sleep is *necessary* for the integration of these synaptic tags, which are an early signature of activity in both subcortical (HC, AMY) and neocortical (PFC) areas [59], to either persist or at least to ensure the progressive rewiring of these networks that support long term memory storage. The outcome is that neural and behavioral markers of selective emotional memory consolidation will be optimal when first, arousal related neuromodulators are elevated around the learning event, and second, sleep occurs shortly thereafter during the consolidation interval (Figure 1).

This model is well grounded in the existing neurobiological literature. Amygdala stimulation and emotional arousal can prolong early-LTP into late-LTP, which requires protein synthesis (e.g. [60]), and pharmacological studies provide evidence for noradrenergic involvement in LTP modulation [61]. Activation of the molecular cascades that regulate protein synthesis could be one

Figure 2



Higher resting cortisol **(a)** or skin conductance response **(b)** at the time of learning was linked to enhanced retrieval of negative, but not neutral, information. Enhanced resting cortisol also was related to **(c)** an increased relation between looking time at encoding and subsequent memory specifically for negative (not neutral) information and **(d)** enhanced activity in the medial PFC (in red) and amygdala (in purple) during retrieval of negative information. These patterns were significant only in those who slept (and not those who remained awake) during the memory delay period.
Figures adapted from [65] (b) and [27•,28] (a, c, and d).

of the functions of norepinephrine, and perhaps other arousal related neuromodulators such as cortisol. In the presence of a temporally related emotional learning event, neuronal metabolism, transcription, and translation may be activated via noradrenergic projections, thus providing the tagged synapses with the proteins required to reinforce and prolong the modification in synaptic efficacy. Synaptic tagging is a cellular phenomenon, yet activation of PRPs may be triggered by emotional events and likely results in the consequent release of arousal-related neuromodulators that enhance connectivity within critical emotional memory circuits (e.g. amygdala, hippocampus, PFC regions). It is therefore a phenomenon that may bridge cellular and systems aspects of memory formation. Thus, synaptic tagging can act as a filter that 'selects' a relevant event, or even a specific aspect of an event, allowing only that information to be subject to the longer time scale of systems consolidation.

Sleep may be the ideal brain state for systems consolidation to occur [62], because it is a protected time that also consists of several unique high frequency stimulation events (spindles, sharp wave-ripple events, theta rhythm) that may help maintain system wide plastic changes over a longer period. Additionally, because there is also cholinergic involvement in LTP modulation [63], the acetylcholine-driven REM sleep state may help boost long-term plastic changes for emotional memories specifically. Thus, once the tags are set during learning, sleep may contribute to the lasting and selective plasticity within emotional memory networks required for long-term emotional memory. Indeed, we have shown previously that optimal emotional memory consolidation occurs when two conditions are met: cortisol levels are elevated *during learning* and sleep takes place during the subsequent consolidation delay ([27•,28]; see Figure 2). Thus, while cortisol benefits effective tagging, increasing the likelihood of long-term plasticity [64], sleep enhances the efficiency with which those tags are executed.

One important consideration is that cortisol has a sluggish timecourse. Thus, although cortisol may provide important background conditions for setting a salience 'tag', there must be a faster signal that denotes salience on a trial-by-trial basis. Indeed, we have demonstrated that trial-by-trial changes in skin conductance responses during learning predict subsequent memory for emotional (but not neutral) information 12hr later, but, again, only if a night of sleep occurred during the delay ([65]; see Figure 2b).

We hypothesize that the sympathetic responses generated by the emotionally arousing stimuli themselves provide a salience signal, and that, along with elevated cortisol during learning, an optimal neurochemical environment for the 'tagging' of these salient portions of an event is achieved. Although this hypothesis still requires direct testing, it is in line with evidence demonstrating that HPA axis and sympathetic activation are essential for emotional memory consolidation (e.g. [66,67]). Consolidation processes, which we hypothesize will be optimized during sleep, would then 'select' these emotionally salient items for preferential processing, leading to long-lasting changes in the neural trace that continue to be reflected at the time of retrieval.

Conclusion

Although separate literatures link sleep and stress to selective emotional memory consolidation, we argue that these brain states interact in critical, indeed necessary, ways to promote selective remembering. Secretion of stress-related and arousal-related neuromodulators at the time of encoding promotes the selective tagging of memories, which is necessary for sleep-based processes to identify the correct representations for reactivation and systems-level memory reorganization. Likewise, sleep soon after encoding is necessary for these stress and arousal promoted tags to achieve a long-lasting impact, because sleep physiology is unique in its ability to promote the high frequency stimulation that we believe promotes the systems level consolidation underlying truly long-term memory. In this cooperative manner, we suggest that stress and sleep, by linking encoding and consolidation processes, and by linking synaptic consolidation to systems consolidation, allow long lasting emotional memories to form and persist.

Conflict of interest statement

None declared.

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- •• of outstanding interest

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