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Stress and Sleep Interact to Selectively Consolidate and Transform Negative Emotional Memories

Implications for Clinical Treatment

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Emotional experiences leave durable traces in the brain and tend to be exceptionally well remembered for long periods of time, if not forever. Robust memory for negative events, however, can be a double-edged sword. On the one hand, our ability to remember and learn from negative experiences is critical for skills ranging from social functioning (learning from a social gaffe so that one doesn't make it again) to physical survival (remembering never to return to the location of a vicious dog that lives down the street). On the other hand, while our bias to remember negative information might be adaptive on the whole, it can also contribute to the etiology and perpetuation of clinical disorders such as depression and anxiety (e.g., Mogg, Matthews, & Weinman, 1987; Wilker, Elbert, & Kolassa, 2013). Recent research makes it clear that to understand how memories for negative events become so indelibly etched in the brain, it is necessary to consider not only the stress and arousal experienced around the time of the emotional event, but also the sleep that occurs thereafter.

In addition to promoting the consolidation and stabilization of emotional memories, however, sleep and stress exposure can also elicit memory *transformation*, which might be beneficial to the clinician looking to modify negative or traumatic memories in cases of depression, anxiety disorder, or posttraumatic stress syndrome (PTSD). On the face of it, the idea that memories might be changeable seems counterintuitive. After all, what use is a memory system that doesn't always accurately reflect the past? Yet a highly rigid memory system capable only of replaying veridical accounts of our past would make it difficult, if not impossible, to update knowledge, to interleave new information with old, to

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use knowledge in flexible ways, to reappraise or reconstrue events in the face of competing information, and to make meaning of our experiences. Such skills are essential for optimal learning and healthy mental functioning, and they are important to consider if our memory systems are to be understood, as new evidence suggests, as predictive and adaptive, allowing us to flexibly use our past experience to predict an ever-changing present and an unknown future (e.g., Schacter & Addis, 2007). This need to use our memories to make predictions about the future and not just to remember, but to make sense of, the past may be why our memories operate less as static entities and more as emergent, dynamic processes that evolve over the minutes, hours, days, and even years following new learning. Far from being instantly solidified in high fidelity as veridical snapshots of our experience, our memories form gradually and change over time. Thus, although the postlearning memory "consolidation" phase is often conceptualized as one of simple memory stabilization, evidence suggests that consolidation (and reconsolidation) processes also *restructure* memories in ways that render them more useful. As I will discuss, this is true for even very negative emotional memories. Because stress and sleep play a role in such memory restructuring, both might be used to strategically modify maladaptive memories in clinical settings.

Although both stress and sleep are important to consider in any discussion of negative emotional memory formation, the literatures examining the impact of stress and stress hormones like cortisol and norepinephrine on our memories on the one hand, and the influence of sleep and the various stages of sleep on the other, have proceeded down largely separate paths. Very few studies have examined how stress and sleep *interact* to influence memory function. This is an important gap in the literature considering the obvious relationships between stress and sleep in our daily lives. As many of us know all too well, bouts of insomnia are often preceded by stressful events, and sleep deprivation is associated with marked elevations in cortisol (e.g., Balbo, Leproult, & Van Cauter, 2010; McEwen, 2006). I refer to this bidirectional relationship as the "sleep–stress snowball," where stress impairs sleep, sleeplessness increases stress, and both disrupted sleep and heightened stress induce changes in memory and compound upsets to emotional balance. The purpose of this chapter is to (a) review the evidence that emotional memory formation is impacted independently by stress and sleep; (b) review recent findings examining how stress and sleep might interact to influence emotional memory formation; (c) present a new model arguing that elevated stress hormones at the time of learning, and sleep during the consolidation interval, are critical for long-lasting emotional memories—both for better and for worse; and (d) suggest implications of this model for treating emotional memory related disorders (e.g., depression, anxiety) in the clinic.

Stress, Stress Hormones, and Emotional Memory Consolidation

Memory consolidation is the process by which newly acquired information, initially fragile, becomes stabilized in long-term memory circuits (Dudai, 2004; McGaugh, 2000). This consolidation process depends on a molecular cascade that leads to structural and functional changes in neurons, both of which are influenced by stress hormones. Such influences on neuronal structure and function are thought to explain why stress exposure often strengthens memory consolidation. The sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis work in concert to enhance memory for emotional information during times of stress (Roozendaal, McEwen, & Chattarji, 2009), reflecting the fact that concurrent cortisol and norepinephrine activity in the basolateral amygdala intensifies functional connectivity and interactions between the amygdala, hippocampus, and other memory-relevant regions of the brain such as the ventromedial prefrontal cortex. Because this network is critical for emotional memory formation, its potentiation by stress hormones is thought to underlie the behavioral effect—that emotional memories are often selectively enhanced, in contrast to neutral ones, under stress (McGaugh, 2004).

The behavioral evidence demonstrating that stress-related neuromodulation selectively intensifies emotional memories is abundant in both rodents and humans (Payne et al., 2004; de Quervain et al., 2009). In rats, stress hormones typically do not globally enhance memory consolidation, but preferentially modulate consolidation of emotionally arousing experiences (e.g., Roozendaal, Okuda, de Quervain, & McGaugh, 2006; Yang et al., 2006; see Roozendaal, Barsegyan, & Lee, 2007; Roozendaal & Hermans, 2017, for reviews). Similarly, in humans, stress exposure facilitates the consolidation of emotionally arousing, relative to neutral, pictures and stories (Buchanan & Lovallo, 2001; de Quervain et al., 2009) and even enhances emotional relative to neutral features within a single complex episode (Payne et al., 2007). For example, Buchanan and Lovallo (2001) demonstrated that a 20 mg dose of cortisol during learning enhanced the consolidation of emotionally arousing, but not nonarousing, pictures. Similarly, Payne et al. (2007) demonstrated that psychosocial stress exposure (which involves giving a speech in front of emotionless judges) enhanced long-term memory for an emotionally arousing slide show relative to a control condition, but impaired memory for a closely matched neutral slide show. Cahill et al. (2003) showed that participants who were exposed to cold-pressor stress (a physical stressor that involves placing one's arm in ice cold water) after watching a slide show consisting of neutral and emotionally arousing slides remembered more emotional slides than nonstressed control participants, whereas memory for neutral sides was unaffected. Abercrombie, Speck, and Monticelli (2006)

demonstrated that while cortisol elevations in humans are often correlated with enhanced memory consolidation for emotionally laden information, this is only the case when individuals are emotionally aroused and thus norepinephrine is presumably elevated.

Underlying these memory effects at a neural level, work in animal models has demonstrated that a level of stress hormones that impairs hippocampal and prefrontal cortex (PFC) structure and function by contrast enhances amygdala function and plasticity. Likewise, human neuroimaging studies demonstrate that cortisol elevations at encoding can diminish hippocampal activity, while potentiating activity in the amygdala. Pruessner et al. (2008) showed that acute stress induced prior to an encoding task provoked significant deactivation in the hippocampus, and the degree of hippocampal deactivation was significantly correlated with cortisol reactivity. Van Stegeren et al. (2007) showed that elevated cortisol levels correlated with intensified amygdala activation at encoding and better future memory for emotional information. Thus, evidence from multiple levels of analysis, from cellular analysis in rodents to functional magnetic resonance imaging (fMRI) studies in humans, has demonstrated that while elevated cortisol often impairs hippocampal and prefrontal cortical function, amygdala function is enhanced (e.g., Ghosh, Laxmi, & Chattarji, 2013; Vyas et al., 2002). Each of these lines of work highlights the importance of stress in the formation of emotional memories.

Interestingly, arousal and stress can enhance emotional memory consolidation regardless of whether exposure directly precedes, directly follows, or occurs during new learning (Hermans et al., 2014), although a new meta-analysis suggests that such effects can be varied (Shields, Sazma, McCollough, & Yonelinas, 2017). One reason for this, especially as it concerns postencoding stress effects, is that sleep has rarely been considered as a mediating factor of stress effects on memory. This is an important oversight to consider given that nearly all studies that report an enhancing effect of stress on emotional memory examine memory after delays of 24 hours or more, which necessitates a period of sleep during the retention interval (Bennion, Payne, & Kensinger, 2017). Indeed, in most studies demonstrating selective emotional memory enhancement by stress, sleep has occurred shortly (i.e., within several hours) after new learning has taken place. This is important given the evidence suggesting that sleep is essential for memory consolidation, which is considered in the next section.

Sleep, Physiological Characteristics of Sleep, and Emotional Memory Consolidation

Multiple levels of analysis suggest that the offline brain state of sleep provides an ideal neurobiological milieu for memory consolidation (see Buzsaki, 2015;

Inostroza & Born, 2013; Walker & Stickgold, 2010, for reviews), including emotional memory consolidation (see Payne & Kensinger, 2010; Walker & van der Helm, 2009, for reviews). At the molecular level, there are several immediate early genes related to synaptic plasticity (e.g., zif-268) that are upregulated during rapid eye movement (REM) sleep in response to manipulations and memory tasks targeting the amygdala and hippocampus (Calais, Ojopi, Morya, Sameshima & Ribeiro, 2015; Ravassard et al., 2016; Riberio, Goyal, Mello & Pavlides, 1999). This is consistent with the notion that sleep constitutes a privileged window for consolidation of emotional memories within larger associative networks (McClelland, McNaughton, & O'Reilly, 1995; Riberio et al., 2007; Hutchison & Rathore, 2015). At the cellular and regional levels, activation patterns seen during daytime task training/encoding in the rat (e.g., Wilson & McNaughton, 1994) and human hippocampus (Peigneux et al., 2004; Oudiette & Paller, 2013) are reactivated during subsequent slow wave sleep (SWS). Moreover, medial temporal regions, including the amygdala and hippocampus, are more active during REM sleep than during wakefulness (Braun et al., 1997; Maquet et al., 1996). 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 neural areas necessary for emotional memory processing. These lines of evidence provide compelling support for an active role for sleep in memory consolidation, as opposed to merely a passive role involving circadian influences or protection from waking interference (Ellenbogen, Payne, & Stickgold, 2006).

Given this evidence, a growing number of studies have utilized postencoding sleep manipulations to examine the memory consolidation process. These studies overwhelmingly support a role for sleep in the long-term storage of emotional episodic information. Numerous studies have shown that sleep benefits memory for neutral episodic memory materials across various modalities, including words and word pairs, pictures, and object–location pairings (see Payne, 2011; Payne, Ellenbogen, et al., 2008; Alger, Chambers, Cunningham & Payne, 2014 for review). Interestingly, however, when emotional (especially emotionally negative) items are intermixed with neutral items at study, sleep disproportionately benefits the consolidation of emotional relative to neutral memories (Payne et al., 2008; Chambers & Payne, 2014; see Payne & Kensinger, 2010, 2018, in press for review). Wagner et al. (2001) reported that memory for negatively arousing relative to neutral narratives was facilitated after 3 hours of late-night, REM-rich sleep known to activate the hippocampus and amygdala, but not following equivalent amounts of time spent awake or in early-night, slow-wave-rich sleep. Similarly, others have demonstrated that a full night of sleep preferentially improves memory accuracy for recognition of negatively arousing pictures

relevant to an equivalent period of daytime wakefulness (reviewed in Walker & van der Helm 2009). These findings strongly suggest a role for sleep in the processing of memory for emotional experiences.

Emotional Aspects of Complex Memories Are Prioritized During the Consolidation Period

The previous sections highlight the importance of stress and sleep in the formation of emotional memories. But precisely which *aspects* of our emotional memories are influenced by stress and sleep? This is an important question to ask, because memories of emotional events are not stored as precise replicas of the original experience, and they typically contain both neutral and emotional features. Thus, it is possible that stress exposure and sleep may preferentially enhance some, but not all, aspects of memory for emotional experiences.

Central, emotionally salient information is typically remembered at the expense of neutral background information (Payne, 2011; Payne, Nadel, Britton & Jacobs, 2004; Payne & Kensinger, 2010; see Reisberg & Heuer, 2004, for a review). This is known as the "emotional memory trade-off effect" (see Payne & Kensinger, 2010, 2018, for reviews). Such trade-off effects in emotional memory are not restricted to the laboratory, but can also be found in the real world. One ecologically relevant example is the weapon-focus effect, where victims vividly remember an assailant's weapon but have poor memory for other aspects of the event, including the face of the perpetrator (Stanny & Johnson, 2000). This divergence in memory for central and peripheral aspects of emotional episodes depends in part on differential attention and encoding of these two aspects of the scene. However, we also know that these aspects undergo qualitatively different processing after encoding, during the consolidation period, particularly if this period includes sleep (e.g., Payne, Stickgold, Swanberg, & Kensinger, 2008; reviewed in Payne & Kensinger, 2010) or exposure to stress (Cunningham et al., 2018).

Payne, Swanberg, et al. (2008) examined how the different components (negative arousing vs. neutral) of complex emotional memories would change across periods of sleep versus wakefulness. It was unclear how the different components would be processed and stored in memory—whether they would change over time or remain the same, and whether a period of sleep would affect their consolidation differently than a period spent awake. Emotional scenes could be stored as intact units, suffering some forgetting over time but retaining the same relative vividness for all components. Alternatively, the individual components of an emotional experience could undergo differential memory processing, perhaps

with a selective emphasis on only what was most emotionally salient and worthy of remembering.

To assess these questions, we presented participants with scenes depicting negative or neutral objects placed on neutral backgrounds at either 9 AM or 9 PM (see Figure 7.1 for example stimuli). Twelve hours later, after a day spent awake or a night of sleep, we tested memory for objects and backgrounds separately, to examine how these individual components of emotional memories change across periods containing a night of sleep or a day of wakefulness (Figure 7.2). We found that daytime wakefulness led to forgetting of the emotional scenes in their entirety, with both objects and backgrounds suffering forgetting at similar rates. Sleep, however, led to a selective preservation of negative objects, but not their accompanying backgrounds, suggesting that the two components underwent differential processing during sleep. This finding demonstrates that, rather than preserving intact representations of scenes, the sleeping brain effectively

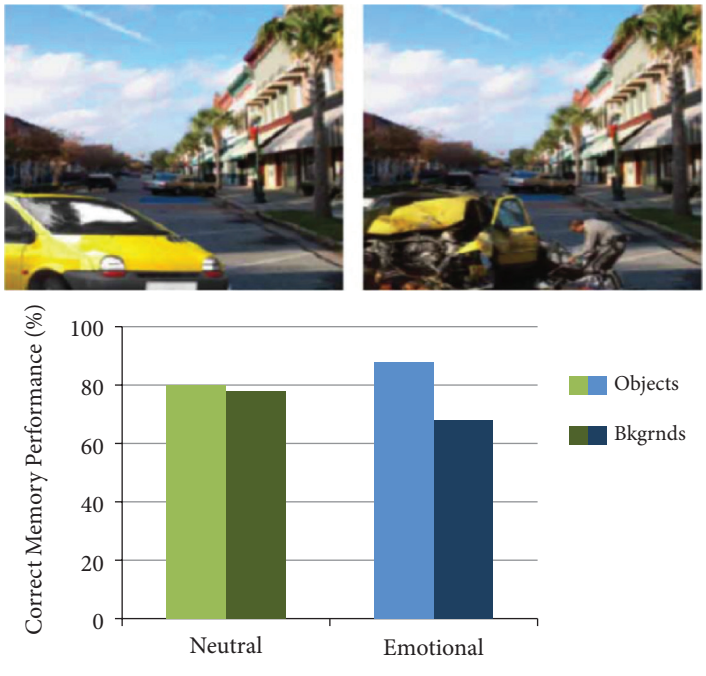

Figure 7.1 Example experimental stimuli (top) and graphical depiction of the trade-off effect as percentage of neutral versus emotionally arousing objects and backgrounds recognized (bottom). Stimuli depicting neutral backgrounds with either a neutral (top left) or negatively arousing (top right) object in the foreground were presented. Participants show increased recognition of emotionally arousing foreground objects with impaired recognition of neutral backgrounds (bkg).

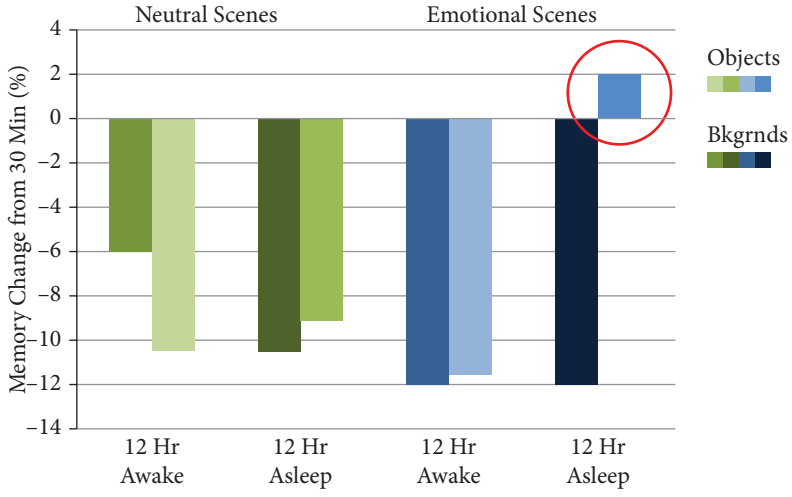

Figure 7.2 Change in recognition memory for neutral and emotionally arousing objects and their associated (neutral) backgrounds after periods of wake versus sleep. Recognition memory for neutral objects and backgrounds (bkg) decreased from 30 minutes posttraining by 6% to 12% across either 12 daytime hours of wakefulness (9 AM to 9 PM) or 12 nighttime hours (9 PM to 9 AM) that included a full night of sleep (minimum of 6 hours of documented sleep time within this time window). Thus, all forms of memory decrease, except for memory for negative emotional objects, which *improved* by 2% over a night of sleep (circled green bar, right).

"unbinds" scenes to consolidate only the most emotionally salient elements (see Payne et al., 2009; Wagner et al., 2004, for additional examples of unbinding during sleep).

To remember an event accurately, as it actually occurred, one must bind its various features together and maintain these intact representations in memory (Mather, 2007). However, sleep does not always consolidate intact representations of experience, instead allowing the individual components of a memory to be flexibly recombined or selectively enhanced at the expense of less important features. REM sleep might be particularly important for such recombination and emotional selectivity (e.g., Payne et al., 2009, 2012; Payne, Swanberg, et al., 2008; Wagner et al., 2004; see Payne, 2011a, 2011b; Lewis, Knoblich, & Poe, 2018, for reviews), at least in overnight sleep designs (see Payne et al., 2015). Unbinding the individual features of a memory is essential for these processes to occur. Determining when and under what conditions sleep preserves memories in veridical form as opposed to restructuring them for selective enhancement or "creative cognition" have become key questions in the field (Lewis, Knoblich,

& Poe, 2018; Payne, 2011a, 2011b; Payne et al., 2009; Payne & Kensinger, 2010, 2018; Walker & Stickgold, 2010).

We have since replicated the finding that sleep selectively enhances emotional components of scene memories in two important follow-up experiments. First, we showed the same selective consolidation of emotional objects in an experiment comparing a daytime nap to two different wake control conditions that strictly controlled for circadian and interference influences (Payne et al., 2015). This study again showed that sleep selectively consolidates emotionally negative aspects of experience, which not only replicated the original result, but also suggested that at least the beginnings of memory consolidation occur after a brief amount of sleep. Second, we have shown that the emotional selectivity effect is further intensified following a 24-hour delay, but only when sleep directly follows encoding of the emotional scenes—not when sleep occurs after a day of wakefulness (Payne et al., 2012). Across this longer delay, emotional object memories continue to be protected (i.e., they do not deteriorate further), but there is additional, and perhaps active, suppression of memory for associated backgrounds. While further work is needed to determine the precise time course of memory consolidation, these data suggest that additional nights of sleep might continue to sculpt the memory trace so that only the most emotionally salient aspects are preserved long-term.

Such results suggest that sleep-mediated consolidation processes help solidify the negative emotional aspects of an experience into a durable memory trace, while allowing the less emotional aspects to deteriorate. This finding may help us understand why memory for central, emotional information is often remembered at the expense of background details (see Figure 7.1; Mather, Clewett, Sakaki, & Harley, 2016; Reisberg & Heuer, 2004). As previously mentioned, a real-world example of such an emotional memory "trade-off" is the weapon-focus effect, where crime victims vividly remember an assailant's weapon but have little memory for other important aspects of the scene. Often these effects have been described in terms of attentional narrowing at encoding. Indeed, having a visually evocative "attention magnet" in a scene can increase the likelihood that such trade-offs occur (Easterbrook, 1959; Reisberg & Heuer, 2004), and neuroimaging studies have implicated the engagement of affective-attentional processes during encoding in the formation of a memory that will only include a subset of the details processed during an event (Kensinger, 2009). Our recent sleep studies, however, emphasize that individual aspects of emotional experiences continue to be altered with the passage of time and are fundamentally influenced by sleep-based consolidation processes. As discussed in the following text, the same is true for stress exposure during the consolidation period.

Like sleep, stress exposure after encoding these scenes leads to the selective consolidation of emotional information. In Cunningham et al. (2018),

participants were exposed to a psychosocial stressor or a matched control condition after encoding the scenes. Stressed participants showed an increase in both subjective reports of stress and physiological stress reactivity as measured by salivary cortisol. Compared to controls, stressed participants showed an amplified emotional memory trade-off effect the next day, which was again defined as a memory enhancement for emotional objects at the expense of memory for the backgrounds on which they were placed, as well as for the neutral objects and their associated backgrounds. Interestingly, we found that high cortisol responders drove this effect, while low responders performed similarly to controls. Because high and low responders both reported significant increases in state anxiety compared to controls, these results suggest that cortisol reactivity, rather than subjective stress more generally, drives the preferential consolidation of emotional information. Rather than influencing all aspects of an experience similarly, elevated cortisol differentially affects memory for the different components of our experiences, selectively benefiting only what is most emotionally salient, and likely adaptive to remember. These results are highly reminiscent of our earlier work (Payne et al., 2006, 2007) demonstrating that stress exposure (relative to a control condition) can enhance long-term memory for an emotionally arousing slideshow, while actually impairing memory for a closely matched neutral slideshow. Because they are also so similar to our studies examining the role of sleep in selective emotional consolidation, the following questions arise. Is a common mechanism involved? And, might sleep and stress interact to preferentially benefit the negative aspects of memory?

Stress and Sleep Interact to Selectively Benefit Emotional Memory Consolidation

As just reviewed, sleep and stress have independently been tied to the selective consolidation of negative emotional memories. But how might they interact? One idea involves the overlap between the elevated cortisol levels that occur during stress/cortisol laboratory-based (exogenous) exposure and the (endogenous) elevations in cortisol that naturally accompany late-night, REM-rich sleep (see Figure 7.3). Both stress and sleep studies thus share elevated cortisol levels in common, and, as we have seen, both produce the same selective emotional memory effect, so might cortisol be the common mechanism? Some evidence supports this idea, at least indirectly. Recall that the selective emotional memory effect is benefitted by an overnight period of sleep (Payne et al., 2009, 2012). When examining the sleep stage correlates of this effect, we found that the magnitude of selectivity in emotional memory was predicted by the amount of

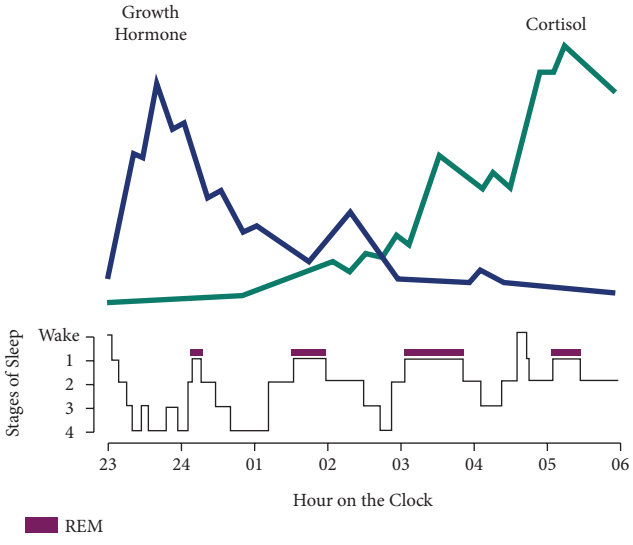

Figure 7.3 The relationship between sleep-stage architecture and circulating levels of growth hormone (in purple) and cortisol (in gray). Note both the linear increase in cortisol across the night and also the cortisol peaks riding on top of rapid eye movement sleep (REM) periods.

REM sleep obtained overnight (Figure 7.4). Given that cortisol tracks REM sleep in its circadian variation, perhaps elevated cortisol is the driver of the correlation pictured, rather than REM sleep per se. Although we do not yet have a firm answer to this question, the idea finds partial support in a study that upregulated

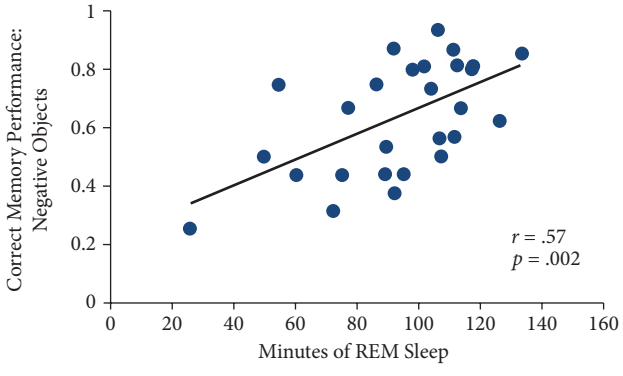

Figure 7.4 Rapid eye movement sleep (REM) sleep correlations. Recognition of negative objects was selectively and positively correlated with time spent in REM sleep (REM sleep min) and with percentage of the night spent in REM sleep (REM sleep %).

cortisol secretion experimentally during a night of sleep (van Marle et al., 2013). These authors administered 20 mg of hydrocortisone prior to a night of sleep, directly following encoding of negative and neutral pictures in a double-blind, placebo-controlled, between-subjects study. Hydrocortisone administration resulted in elevated cortisol levels throughout the night and led to prioritization of emotional over neutral memory consolidation. However, this effect was not REM-sleep dependent, and other studies have failed to show such a clear, emotional memory specific, effect (Wagner et al., 2005; Wilhelm et al., 2011). Clearly, more research is needed if we are to understand the effect of nocturnal cortisol on REM sleep-emotional memory relationships.

Distinct from this is the idea that stress hormone release that occurs, not *during* sleep, but rather *prior* to sleep, around the time of encoding (e.g., just before, just after, or during the learning event), sets the stage for downstream selectivity in sleep-based memory consolidation, and this in turn leads to the persistence of emotional aspects of memories (Dudai & Morris, 2000). In

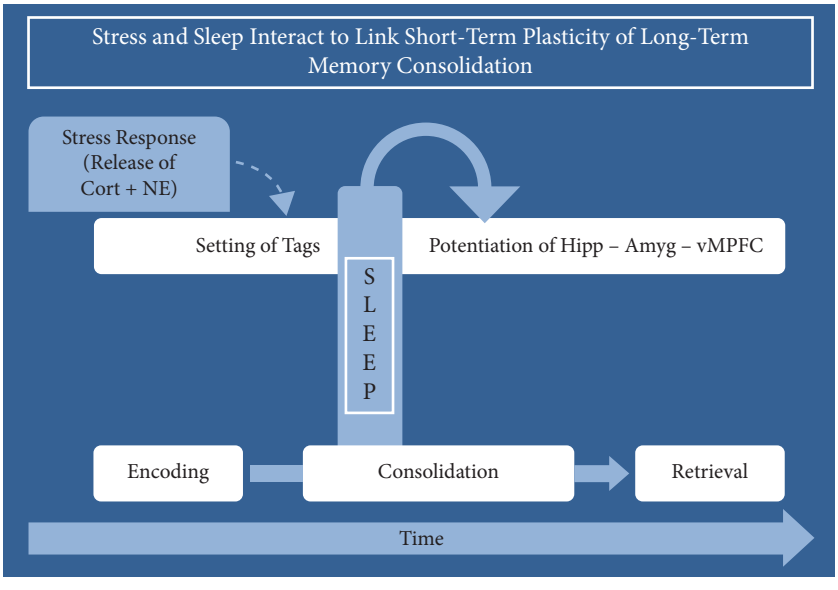

Figure 7.5 During an emotional experience, stress-related and arousal-related neuromodulators are released. Their presence helps set molecular tags that mark key features of an emotional experience. The unique, high-frequency stimulation that occurs during postlearning sleep (e.g. hippocampal sharp wave ripples, sleep spindles, theta rhythm) further potentiate these changes, helping to translate synaptic changes into the long-lasting changes that underlie systems memory consolidation.

the section that follows, I propose a model (Figure 7.6) that makes two novel predictions about how these interactions between encoding and consolidation occur. First, I argue that arousal-related neuromodulators (i.e., norepinephrine and cortisol), when released around the time of new encoding, help set molecular "tags" that designate specific traces of emotional information within an event to be prioritized for consolidation. Importantly, the very concept of a "tag" seeks to explain how neural signaling creates a target for subsequent plasticity-related products (PRPs) that are essential for sustained and *selective* plasticity in neural circuits. These tags, which are set during or near the learning event (Moncanda, Ballarini, & Biola, 2015; Wang & Morris, 2010), ensure memory specificity by guaranteeing that PRPs required for memory stabilization are captured only by

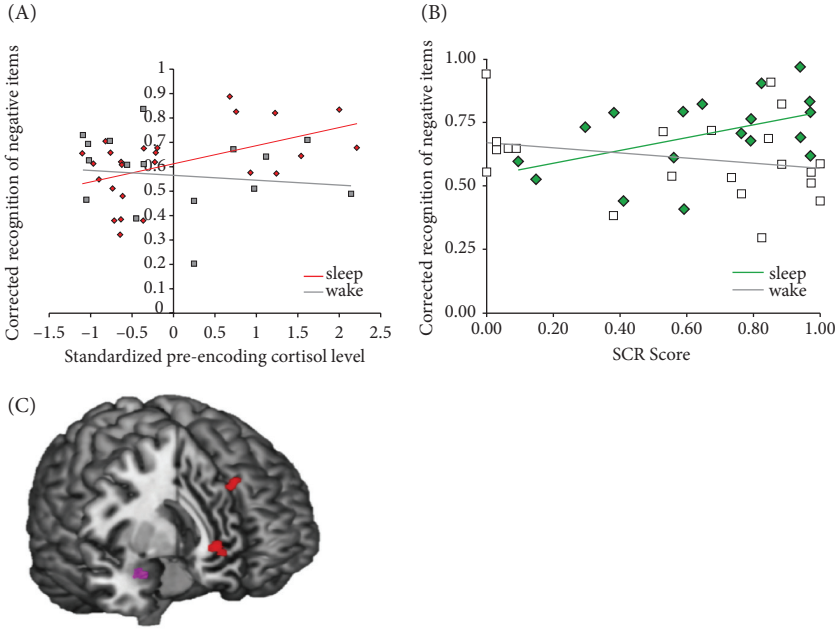

Figure 7.6 Higher resting cortisol (A) or skin conductance (B) at the time of learning was linked to enhanced selective consolidation of negative, but not neutral, information. Enhanced resting cortisol was also related to (C) an increased relation between looking time at encoding and subsequent memory specifically for negative (not neutral) information and (D) enhanced activity in the medial prefrontal cortex (in red) and amygdala (in purple) during retrieval of negative information. These patterns were significant only in participants who slept (and not those who remained awake) during the memory delay interval.

Source: Figures adapted from Bennion et al. (2015), Bennion, Payne, and Kensinger (2015), and Cunningham et al. (2014).

activated aspects of representations and not by other aspects, thereby setting the stage for selective emotional memory consolidation to occur. This initial stabilization process enables the relevant representations to retain their strength for at least several hours, which is long enough to support the limited lifespan of molecular tags (Martin & Kisik, 2002) and also for sleep to occur. At this point, sleep-based consolidation processes act on those specific, tagged representations (but not others). Although we cannot measure these tags directly in humans (and, indeed, their molecular identity is unknown), I argue that evidence of these tags exists in strengthened connectivity among brain regions that are essential for emotional memory—the amygdala, hippocampus, and ventromedial PFC—as well as in improved behavioral performance (i.e., behavioral tagging, Dunsmoor, Murty, Davachi, & Phelps, 2015) for emotional relative to neutral content (Figure 7.5).

Second, and critically, the model argues that the unique high frequency stimulation and reactivation that occurs during postlearning sleep is essential for linking these distributed tags into the integrated memory trace that allows long-lasting systems consolidation to occur. In other words, sleep is *necessary* for the linking of these synaptic tags, which are an early signature of activity in both subcortical (hippocampus, amygdala) and neocortical (PFC) areas (Kitamura et al., 2017), allowing the tags to persist long enough to ensure progressive rewiring within long-term memory storage networks. 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 time of encoding, and second, sleep occurs shortly thereafter during the consolidation interval (Figure 7.6).

This model is well grounded in the existing neurobiological literature. Amygdala stimulation and emotional arousal can prolong early long-term potentiation (LTP) into late LTP, which requires protein synthesis (e.g., Frey et al., 2001), and pharmacological studies provide evidence for noradrenergic involvement in LTP modulation (Ikegaya et al., 1997). Activation of the molecular cascades that regulate protein synthesis could be one 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 processes 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 (Diekelmann & Born, 2010), 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 (Banks, Warburton, Brown, & Bashir, 2014), the acetylcholine-driven REM sleep state may help boost long-term plastic changes for emotional memories specifically. Thus, once the tags are set during the initial emotional event, sleep may contribute to the lasting and selective plasticity within emotional memory networks required for long-term emotional memory. Indeed, in a recent study, we demonstrated 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 (Bennion, Mickley, Steinmetz, Kensinger, & Payne, 2015; Bennion, Payne, & Kensinger, 2015; see Figure 7.6). Thus, while cortisol enhances the tagging process at the time of new learning, thereby increasing the likelihood of LTP (Morris, 2006), sleep enhances the efficiency with which those tags are executed, facilitating longer lasting connective plasticity in the appropriate amygdala–hippocampus–cortical memory circuits.

One important consideration is that cortisol has a sluggish time course, taking roughly 20 to 30 minutes to peak following exposure to a stressor (although note that cortisol also has rapid, nongenomic effects on neuronal activity in humans; Schilling et al., 2013; Strelzyk et al., 2012). 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 12 hours later, but again, only if a night of sleep occurred during the consolidation delay (Cunningham et al., 2014; see Figure 7.6B).

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., Abercrombie, Speck, & Monticelli, 2006; Roozendaal et al., 2006). Consolidation processes, which we believe are optimized during sleep, would then "select" these emotionally negative aspects of experience for preferential

processing, leading to long-lasting changes in the neural trace that continue to be reflected at the time of retrieval.

Too Much of a Good Thing?

Thus far, I have largely been discussing selective emotional memory "benefits" and implying that negative emotional memory consolidation is a good thing. First, I should note that we do observe selective emotional memory consolidation for positive memories as well (Chambers & Payne, 2013, 2014), although the effects are typically not as strong as those for negative memories (which might be due to difficulties associated with finding a sufficient number of positive images that are also highly arousing; Payne & Kensinger, 2010). Second, I would argue that our ability to remember our negative experiences, while often painful or embarrassing, is adaptive. If we did not remember our mistakes and our negative encounters in the world, we would not be able to learn, change, adapt, and grow from them. So selective memory for negative events and information is a good thing, at least up to a point. Nevertheless, affective disorders such as depression and anxiety are associated with negative memory biases. So, what is the difference between a "selective negative memory benefit" and a "negative memory bias"? In the short term, perhaps there is no difference. Being predisposed to recall the negative is most likely an evolutionary adaptation, as it is essential for survival at a species level, as well as for learning about the environment at the individual level. But is it possible to have too much of a good thing? I would argue that it is possible and that precisely this excessive processing of negative information is what marks many mental health conditions. Numerous authors have argued that negative memory biases contribute to the etiology and perpetuation of affective disorders (e.g., Mogg, Matthews, & Weinman, 1987; Wilker, Elbert, & Kolassa, 2013). While it is obviously beneficial to pay special attention to negative threats in one's environment during times of stress, what is adaptive in the short term may become problematic and maladaptive in the long term. This is the difference between a stressful period that leads to negativity for a few days versus persistent stress that leads to long-lasting and excessive negativity or between a night or two of insomnia that naturally resolves itself versus long-lasting insomnia that perpetuates high levels of stress and impaired emotional processing over the long run. Of note, early life stress and trauma, both of which impact cortisol reactivity and sleep (Lupien, McEwen, Gunnar, & Heim, 2009; Kajeepeta, Gelaye, Jackson, & Williams, 2015) and thus likely the consolidation mechanisms I have been discussing, have a profound effect on the tendency to develop maladaptive emotional and behavioral patterns that lead people to seek psychotherapy. In this sense, a negativity bias, or an excessive focus on and memory for the negative,

may not only be what brings people to therapy in the first place, but also what the therapist needs to work to modify during treatment.

Although a thorough discussion of the clinical interrelationships between sleep, stress, and cognitive biases is beyond the scope of this chapter, it is worth noting that both depression and anxiety disorders (e.g., PTSD) are associated with impaired sleep, disrupted stress regulation, and excessively negative memory (Cunningham, Pardilla-Delgado, Alger, & Payne, 2014; Payne et al., 2004). In addition to the negative information and memory biases already mentioned, HPA axis and cortisol regulation is impaired in many affective disorders, as is sleep stage architecture. For example, major depression is often characterized by persistently elevated cortisol levels, altered diurnal regulation of cortisol, and excessive amounts of REM sleep that also occur too early in the nocturnal cycle (Tsuno et al., 2005). These changes in REM sleep may disproportionately amplify the strength of negative memory consolidation leading to the common occurrence of a negativity bias of memory for those with the diagnosis (Pyszczynski et al., 1989). REM sleep disturbance and nightmares, as well as increased sympathetic autonomic tone, are also common features of PTSD (Mellman et al., 1997; Lavie, 2001). Thus, therapeutic methods have been designed to target each of these areas of dysregulation. Cognitive-behavioral therapy (CBT) helps people learn new ways of thinking and behaving that can reduce negativity, and cognitive behavioral therapy specifically for insomnia (CBT-I) addresses unhealthy thoughts and behaviors related to sleep that help ameliorate insomnia. Relaxation training and mindfulness-based stress reduction techniques have been successfully used to lower cortisol levels and improve sleep (Brand, Holsboer-Trachsler, Naranjo, & Schmidt, 2012). Moreover, treating insomnia early might stave off depressive episodes, and it is interesting that most antidepressant medications reduce REM sleep.

Although the focus of this chapter has been on memory consolidation, it should be noted that stress and sleep also influence memory reconsolidation (see Chapters 2 and 14 in the volume for a review). As has been implied in this chapter, consolidation does not result in memory representations that are immutable. Memories are indeed stabilized and strengthened during the consolidation process, but they can also be qualitatively altered when recollected or reactivated. Although the dynamic and flexible nature of our memories do make us prone to memory errors (Bartlett, 1932; Bergman & Roediger, 1999), such changeability also provides a mechanism for updating existing knowledge with new information and making meaning of our experiences by understanding them in a new light. Indeed, in Payne (2011), I have argued that although reactivation during SWS leads (in most cases) to memory stabilization and enhancement, REM sleep is largely responsible, not just for emotional memory modification,

but perhaps for all major memory restructuring (see Figure 7.7). This raises the question of whether napping after a successful therapy session (e.g., one that begins the process of corrective emotional experience) is advisable. Future work should carefully examine this question, as it is certainly possible that a 90-minute posttherapy nap (90 minutes constitutes a full sleep cycle and thus includes REM sleep) might benefit efforts to target and change maladaptive emotional memories. Another option, which would harness the potential power of a full night of sleep (rather than a daytime nap) would be to give a patient "reminder

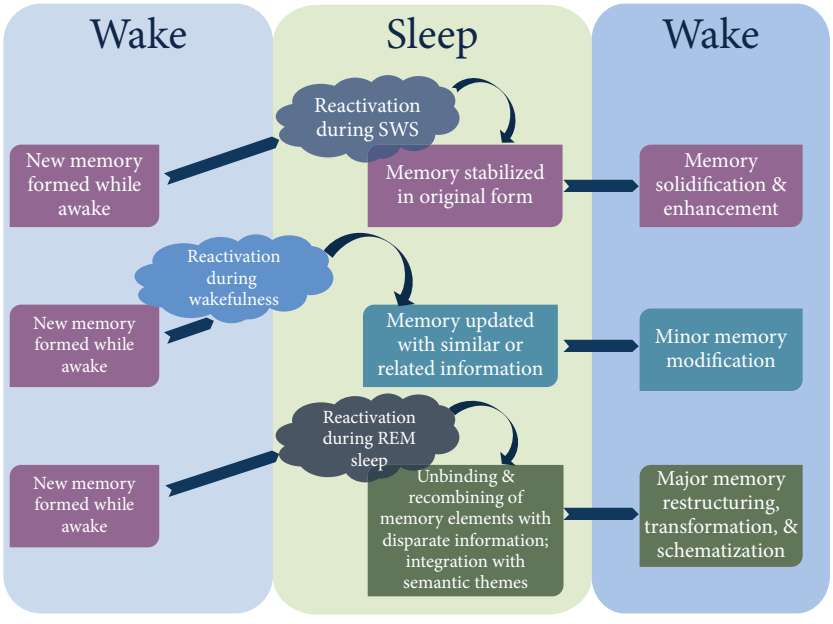

Figure 7.7 Potential influence of memory reactivation during wakefulness and different stages of sleep. Top: reactivation during slow-wave sleep (SWS) causes enhancement and stabilization of memory in its original form, leading to memories that are largely true representations of originally encoded experience. Reactivating memories during SWS by representing a memory cue (such as an odor) present at initial learning leads to memory stabilization (Diekelmann et al., 2011). Middle: reactivation during wakefulness causes memory modification and updating, allowing new but related information to be incorporated into the original memory trace (Lee, 2009; Hupbach et al., 2007). Bottom: reactivation during rapid eye movement (REM) sleep causes substantial memory restructuring and recombination of memory fragments that become isolated in the REM sleep brain state. Such recombination may lead to insight (emotional or otherwise), meaning making, creative problem-solving, and memory schematization.
Source: Figure adapted from Payne (2011).

homework," which should be designed to reactivate the memory of the successful therapy session just prior to going to bed at night. As opposed to our studies of *nocturnal* sleep (e.g., Payne et al., 2012), however, our nap studies suggest that it is not REM sleep, but instead the time spent in SWS during naps, that corresponds to emotional memory processing (Alger et al., 2018; Payne et al., 2015). Drilling deeper into the sleep-based mechanisms of memory consolidation, we find that emotional memory processing is strongly correlated with SWS sleep spindles, which are the thalamically generated bursts of activity (11–15 Hz) believed to promote the brain plasticity that is essential for memory (Buzsaki, 1996; Pavlides & Winson, 1989). These results suggest that while emotional memory processing can result from either a nap or from overnight sleep, the underlying mechanisms are likely different and that brief (approximately 20-minute) posttherapy power naps might provide equal or greater benefit to patients.

These intriguing questions aside, nocturnal REM sleep must operate properly, not only for effective emotional memory processing and emotion regulation to occur, but also for the widespread neocortical connections and memory restructuring needed to "make meaning" out of negative and traumatic events. Thus, proper balancing of REM sleep will likely play a significant role in recovery in the clinic, especially if brain stimulation (i.e., in the gamma range) during REM sleep turns out to promote lucid dreaming (see Voss et al., 2014), where a traumatized patient suffering from repetitive nightmares might be able to gain control over the dream in order to change the outcome (Payne, 2014).

Given these findings, which clearly point to important interactions among sleep, stress, emotional processing, and mental health, there is ample room for new discoveries in the domains of both mechanism and treatment. Just by beginning to appreciate the role of stress and stress hormones in affective disorders (e.g., Keller et al., 2017), and viewing sleep disruption as a potential cause of ensuing depressive or anxiety episodes, rather than just a symptom of them (e.g., Turek, 2005), has been a good place to start. Developing a new treatment that targets all three areas (sleep, stress, emotional memory processing) would likely be revelatory.

Conclusion

Although separate literatures link sleep and stress to preferential emotional memory consolidation, I have argued that the underlying brain mechanisms associated with stress and sleep interact in critical, indeed necessary, ways to promote selective emotional remembering. Secretion of stress 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 most salient representations for cellular 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 contribute the high frequency stimulation that promotes systems level consolidation of long-lasting, selective memories. In this interactive manner, stress hormones 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. However, when stress and sleep become dysregulated, they may interact to promote the excessive emotional memory processing seen in affective disorders, which makes stress neuromodulation and sleep/sleep physiology excellent targets for the development of new clinical therapies for depression and anxiety disorders.

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