Slow oscillation-spindle coupling impairs emotional memory consolidation following stress

Dan Denis[1], Sara Y. Kim[1], Sarah M. Kark[2], Ryan T. Daley[3], Elizabeth A. Kensinger[3], and Jessica D. Payne[1]

[1] Department of Psychology, University of Notre Dame

[2] Department of Neurobiology and Behavior, Center for the Neurobiology of Learning and Memory, University of California, Irvine

[3] Department of Psychology and Neuroscience, Boston College

Abstract

Sleep and stress have both been shown to enhance emotional memory consolidation. They also interact, with the largest benefit of sleep on emotional memory being seen when stress occurs either shortly before or after memory encoding. Slow wave sleep (SWS) is believed to be critical for episodic memory consolidation, facilitated by the coupling of slow oscillations and sleep spindles. However, prior work in humans has only demonstrated slow oscillation-spindle coupling to be associated with consolidation of neutral information in non-stressed participants. Whether coupling interacts with stress to facilitate emotional memory consolidation is unknown. To address this exploratory question, we reanalyzed an existing dataset of N=64 individuals. Participants underwent a psychosocial stressor (n=32) or comparable control (n=32) prior to the encoding of 150 line drawings of neutral, positive, and negative images. All participants then slept overnight with polysomnographic recordings. The next day, they were given a surprise memory test. In the stress group, percentage of time spent in SWS was positively correlated with memory for images of all valences (all $r>.35$, $p<.043$). Results were primarily driven by those who showed a high cortisol response to the stressor (all $r>.65$, $p<.007$), compared to low cortisol responders (all $r<.31$, all $p>.25$). However, the amount of slow oscillation-spindle coupling during SWS was *negatively* associated with neutral ($r=-.45$, $p=.01$) and emotional ($r=-.66$, $p<.001$) memory in the stress group. The negative association with emotional memory was significantly stronger than for neutral memory (Meng z=2.04, $p=.04$). Between stress and control groups, there were no differences in any of the sleep measures assessed. These results highlight the importance of considering sleep microarchitecture events in addition to overall sleep stage time and suggests that stress may alter the relationship between SWS and memory consolidation.

Keywords

Sleep, stress, consolidation, emotion, sleep spindles

Introduction

Sleep aids in the consolidation of episodic memory (Diekelmann & Born, 2010; Payne, Ellenbogen, et al., 2008; Rasch & Born, 2013; Stickgold, 2005). One of the main theoretical accounts of this process, the active system consolidation theory, posits that across sleep, memories become less dependent on the hippocampus and more dependent on neocortical areas (Klinzing et al., 2019; Takashima et al., 2006). According to this theory, memory consolidation occurs primarily during periods of slow wave sleep (SWS) and is facilitated by the precise triple phase-locking of neocortical slow oscillations, thalamocortical sleep spindles, and hippocampal sharp-wave ripples (Klinzing et al., 2019; Rasch & Born, 2013). Evidence for this triple-phase locking, and its importance for memory has emerged with rodents (Latchoumane et al., 2017). In humans, this coordination has been demonstrated in epilepsy patients with intracranial hippocampal recordings (Staresina et al., 2015). Although hippocampal ripples cannot be detected non-invasively, slow oscillation-spindle coupling as detected via scalp EEG has been associated with memory consolidation in healthy humans (Denis et al., 2020; Mikutta et al., 2019; Niknazar et al., 2015; Zhang et al., 2020).

Notably, there is substantial evidence that some memories are more likely than others to be consolidated during sleep (Diekelmann et al., 2009; Stickgold & Walker, 2013). Emotional valence acts as a prioritization cue in the selective consolidation of both negative (Nishida et al., 2009; Payne et al., 2015; Payne, Stickgold, et al., 2008) and positive (Chambers & Payne, 2014a, 2014b; Kim et al., 2020) episodic memories (Lipinska et al., 2019; Payne & Kensinger, 2010). Although much research has linked the consolidation of emotional memories to rapid eye movement sleep (Groch et al., 2013; Kim et al., 2019; Nishida et al., 2009; Payne et al., 2012; Payne, Stickgold, et al., 2008; Sopp et al., 2017; Wagner et al., 2001), newer work suggests SWS plays a role as well (Alger et al., 2018; Kim & Payne, 2020; Payne et al., 2015). In fact, several studies have found relationships between emotional memory and SWS but not REM sleep, raising the question of whether SWS and REM sleep differentially contribute to emotional memory consolidation (Benedict et al., 2009; Payne, 2011,, 2014; Payne et al., 2015; Wagner et al., 2002). The positive effects of SWS have often been shown in daytime naps rather than overnight designs (e.g. Alger et al, 2018; Payne et al, 2015), raising the possibility that sleep stages act differently on emotional memories depending on time of day (Alger et al., 2018).

Others suggest a complementary role for the two stages in emotional memory consolidation, whereby the SWS-REM cycles that naturally occur in overnight sleep serve to strengthen and integrate newly acquired emotional memory traces in preexisting memory networks (Cairney et al., 2015).

In spite of these findings implicating SWS in emotional memory consolidation, the role of SWS-based oscillatory activity, including slow oscillation-spindle coupling, remains underexplored in regard to emotional memories. Research on slow oscillation-spindle coupling has focused almost exclusively on episodic memories for neutral information (though Latchoumane et al. (2015) employed a fear conditioning paradigm in rodents). A key distinction between neutral and emotional memory formation is the involvement of the amygdala (Payne & Kensinger, 2018). While theories of memory consolidation highlight dialogue between the hippocampus and neocortex during SWS as being involved in memory consolidation, interactions between the hippocampus and amygdala, and their relevance for behavior, is currently underexplored (though see Cox et al, 2020). Furthermore, many studies examining SWS in relation to memory focus exclusively on sleep stage correlations. Although broad sleep stage information provide insight into sleep's role in memory consolidation, they fail to capture the neural activity that may more directly underlie consolidation processes during sleep. It is therefore important to consider both broad sleep stage macroarchitecture and the specific neurophysiological “micro” events when investigating the impact of sleep on memory.

Although recent theories (Hutchison & Rathore, 2015) and empirical studies (Kim et al., 2019; Nishida et al., 2009; Sopp et al., 2017) of REM sleep and emotional memory consolidation have examined EEG characteristics during REM sleep (e.g. REM theta (4-7Hz) activity), to our knowledge no studies in humans have assessed the role of slow oscillation-spindle coupling during SWS in emotional memory consolidation. Despite some research finding positive associations with sleep spindle activity and emotional memory consolidation (Alger et al., 2018; Cairney et al., 2014; Cellini et al., 2016; Kaestner et al., 2013) many other studies report no association (Baran et al., 2012; Bennion et al., 2015; Bolinger et al., 2018; Göder et al., 2015; Payne et al., 2015; Prehn-Kristensen et al., 2011). Given the likelihood that it is the *coupling* between spindles and slow oscillations that are important for consolidation processes, this may

explain some of the mixed findings when assessing sleep spindles in isolation. Mechanistically, the coupling of spindles to slow oscillations has been suggested to be crucial to the induction of synaptic plasticity that underlies the formation of long-term memory representations in cortical networks (see Klinzing et al, 2019 for a recent review). Because research on the relationship between slow oscillation-spindle coupling and emotional memory does not yet exist, exploratory work assessing these associations is important if we are to more fully understand how emotional memories are consolidated during sleep. Exploring these relationships is one of our main goals here, as we attempt to better understand the relationship between features of SWS and emotional memory.

A second goal involves better understanding how stress interacts with sleep to benefit emotional memory (Bennion et al., 2015; Kim & Payne, 2020; Payne & Kensinger, 2018). When it comes to the selective processing of emotional memories, sleep is not the only state important for consolidation. Exposure to stress, and stress-related neuromodulators such as norepinephrine and cortisol, have been linked to better subsequent memory for emotional compared to neutral stimuli (Cunningham et al., 2018; Payne et al., 2007; Shields et al., 2017). When these neuromodulators are present around the time of the initial encoding event, changes are triggered in brain regions relevant for emotional memory, including enhanced activity in and connectivity between the hippocampus, amygdala, and prefrontal cortex (PFC) (Ghosh et al., 2013; Vaisvaser et al., 2013; Veer et al., 2011, 2012). Critically, these stress induced changes in neural activity and connectivity are associated with selective enhancement of emotional memory (Schwabe, 2017; Shields et al., 2019).

Psychosocial stress has been shown to lead to alterations in subsequent sleep. In particular, one review highlighted a number of changes in sleep architecture following stress, including reductions in SWS and REM sleep duration (Kim & Dimsdale, 2007). More recently it has been shown that a post-stress nap shows reduced delta (0.5 - 4.5Hz) power compared to a control nap (Ackermann et al., 2019). A small but growing body of work has shown sleep and stress interact to facilitate emotional memory consolidation (Payne & Kensinger, 2018; Kim & Payne, 2020 for review). Levels of cortisol during encoding have been positively correlated with subsequent memory after nocturnal sleep, but not after an equivalent period of daytime wake (Bennion et al.,

2015). This relationship is stronger for emotional memory compared to neutral memory (Bennion et al., 2015). In a different analysis of the dataset reported on here, where stress prior to encoding was induced in half of the participants, theta oscillations (4-7Hz) during REM sleep predicted emotional memory in stressed participants, particularly those showing a high cortisol response following the stressor (Kim et al., 2019). These results suggest that elevations in stress-related neuromodulators during learning aid in the tagging of emotional memories, potentially via enhancement of amygdala-hippocampus-PFC connectivity, for preferential processing during sleep (Kim & Payne, 2020).

An important next step for understanding stress-sleep interactions in emotional memory consolidation is examining the potential impact of stress on oscillatory activity during SWS. Again, by investigating slow oscillation-spindle coupling, we can further understand how sleep physiology subserves not only memory for different types of encoding materials (neutral vs emotional memories), but also different types of encoding conditions (stressed or not). Here, we utilized a rich dataset containing a stress manipulation, overnight sleep with polysomnography, fMRI recordings (not utilized in the present report), and an emotional memory task. This dataset has previously been analyzed in studies of encoding-related changes in resting state functional connectivity in non-stressed control subjects (Kark & Kensinger, 2019a), effects of physiological arousal on emotional memory vividness (Kark & Kensinger, 2019b), repetition suppression effects in non-stressed control subjects (Kark et al., 2020), and interactions between stress and theta activity during REM sleep (Kim et al., 2019). In an attempt to answer our specific questions about interactions between stress and slow wave sleep, we conducted exploratory analyses on this dataset with the goal of answering the following questions:

1. Does time spent in SWS correlate with memory for emotional items (Payne et al., 2015), neutral items (Groch et al., 2015), or both emotional and neutral items?

2. Does slow oscillation-spindle coupling correlate with memory for neutral items, as in previous research (e.g. Mikutta et al., 2019), and does coupling also correlate with emotional memory?

3. Does stress exposure at the time of learning alter these relationships, perhaps by making it even more likely that emotional memories will be consolidated over neutral ones?

Methods

Participants

We analyzed data from a multi-day experiment designed to examine the effects of stress and sleep on emotional memory (see Kim et al., 2019; Kark & Kensinger, 2019 for other analyses of this dataset). In total, 65 participants (ages 18-31, M = 21.86, SD = 2.75) took part in the study. One participant was excluded due to a recording error. Participants were assigned to either the stress (n = 32, 19 female; M_{age} = 21.5 years, SD = 2.8) or control (n = 32, 15 female; M_{age} = 22.3 years, SD = 2.7) condition. Participants reported no history of neurological, psychiatric, or sleep-related disorders, and were free of any other chronic medical conditions or medication affecting the central nervous system. Participants were compensated for their time. The study received ethical approval from the Boston College Institutional Review Board.

Materials

Trier Social Stress Task (TSST)

This task is a reliable, well-validated inducer of psychosocial stress. Participants in the stress group were given 10 minutes to prepare a five-minute speech on a topic (e.g. “Why are you the best candidate for a job?”) using information about themselves. They were told that they would give the speech to two judges and were given writing materials to prepare notes. At the end of the 10 minutes, participants were escorted to a separate room with two seated judges (confederates). Participants then had their notes taken from them and were asked to give the speech from memory. The confederate judges were instructed to keep neutral expressions throughout the speech. If participants completed the speech before the five minutes were up, they

were told to continue. Following the speech, participants performed an arithmetic task aloud for five minutes (e.g. “Continuously subtract 13 from the number 1022 as quickly and accurately as possible”). If they made a mistake, they were told to restart from the beginning.

Participants in the control group performed a similar set of tasks, but designed to minimize psychosocial stress. They had 10 minutes to prepare for the speech task as well, but were informed they were in the control group to mitigate anticipatory stress. They were then escorted into the same room, but without recording equipment (though physiological measures were still taken). They then read their speech aloud in the empty room. After five minutes, they completed an arithmetic task in the empty room.

Emotional memory task

Stimuli were 300 International Affective Picture System (IAPS) images and their corresponding line drawings (Kark & Kensinger, 2015). The use of line drawings was motivated by several reasons: 1) minimize confounds due to re-encoding during the recognition phase; 2) allow cueing of specific memories of the full color image without representing the images themselves; 3) minimize arousal effects during recognition by using retrieval cues that were less emotionally arousing than the images presented at encoding; 4) create a challenging recognition task with sufficient hit and false alarm rates for calculating memory scores.

Negative and positive images were preselected using the IAPS normative database for arousal and valence. Critically, negative and positive images were matched on arousal and absolute valence, and were both more arousing and more negative/positively valanced than neutral images (Kark & Kensinger, 2015).

Procedure

For up to seven days prior to the experimental period, participants wore a wrist actigraphy monitor and kept a sleep log to monitor their sleep schedule. In the 24 hours before participation, participants were asked to refrain from caffeine, alcohol, and tobacco. To avoid contamination of

cortisol samples, participants were told to refrain from physical activity, eating, drinking liquids aside from water, smoking, and brushing their teeth in the two hours prior to the study, and refrain from drinking water for at least 15 minutes prior to the study.

Upon arrival to the laboratory, participants provided a saliva sample for baseline cortisol levels (see Kim et al., 2019 for full details on saliva sampling or cortisol measurement). Participants were assigned to a group, and completed either the stress (TSST) or control task. This was then followed by two further saliva samples taken approximately 15 minutes apart. (Additional saliva samples were taken later in the day to monitor circadian rhythms but will not be discussed further). Then, they completed the encoding portion of the incidental emotional memory task during an fMRI scan. Participants then left the lab and went about their day before returning for overnight sleep monitoring that evening. Participants were instructed not to sleep in this intervening period. All participants slept in the lab with polysomnographic recording. The following day (approximately 24 hours following encoding), participants completed a surprise recognition task, again in the MRI scanner (The study protocol as relevant to the current study is shown in **Figure 1A.** The full protocol is shown in **Supplementary Figure 1**).

Encoding

During incidental encoding, participants viewed 150 negative (50), neutral (50), and positive (50) images. The images that were viewed, versus those held out as foils on the recognition task, were varied across participants. Each line drawing was presented for 1.5s, followed by the full color image for 3s. After viewing each image, participants indicated whether they would approach or back away from the scene if they encountered it in real life. This incidental encoding task facilitates deep encoding. Between each trial, a fixation cross was displayed for 6 - 12s (**Figure 1B**).

Polysomnography

Polysomnography (PSG) was acquired for a full night of sleep for all participants. PSG recordings included electrooculography recordings above the right eye and below the left eye,

electromyography from two chin electrodes (referenced to each other), and electroencephalography (EEG) recordings from six scalp electrodes (F3, F4, C3, C4, O1, O2), referenced to the contralateral mastoids. Data were collected using a Grass Aura amplifier and TWin software at a sampling rate of 200Hz. Following acquisition, data were sleep scored in accordance with American Academy of Sleep Medicine (2007) guidelines. Data were artifact rejected using automated procedures in the Luna toolbox. Artifact free segments of data were subjected to further spectral analyses (see below). One participant had their sleep data removed due to a corrupted file.

Recognition

Participants viewed only the line drawings during the recognition task. All 300 line drawings (100 negative, 100 neutral, 100 positive) were shown to every participant. One hundred fifty were the previously studied items, and 150 were new line drawings, with the encoding lists varying which items were to be classified into each of these categories. Each line drawing was presented for 3s. For each item, participants judged whether an item was: 0 = New, 1 = Old-Not vivid, 2 = Old-Somewhat vivid, 3 = Old-Vivid, 4 = Old-Extremely vivid. Between trials, a fixation cross was displayed for 1.5 - 9s (**Figure 1B**).

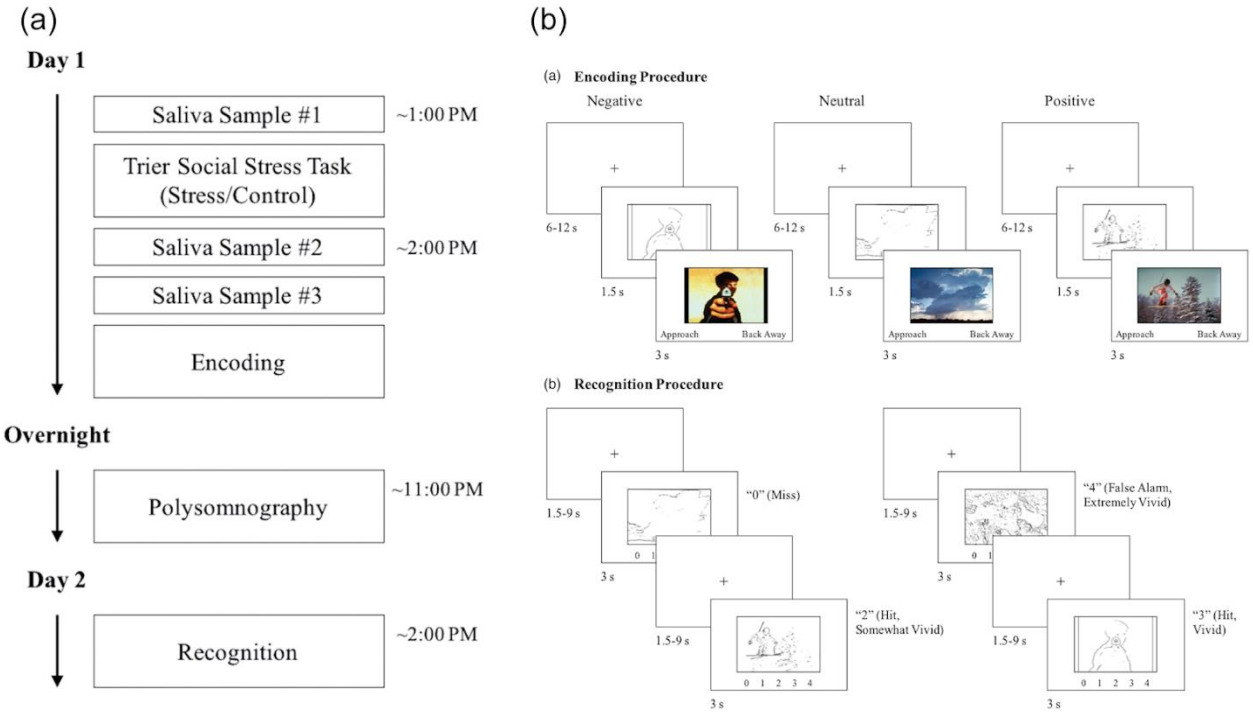

Figure 1. Study timeline and stimuli. **A** – Protocol details of relevance to the current analyses. On day 1, participants underwent the Trier Social Stress Task or control, then completed the encoding task. All participants then slept overnight in the lab with PSG recording. On day 2, participants completed a surprise recognition test. **B** - Encoding/retrieval task. During encoding (top), each line drawing was shown for 1.5s followed by the full IAPS image for 3s. Participants made an incidental encoding judgement (approach or back away) after each image pair. During recognition (bottom), each line drawing was shown for 3s, followed by an old-new judgement and vividness rating. IAPS = International Affective Picture System. Figure adapted from Kim et al. (2019). With permission from Wiley Periodicals, Inc.

Sleep spectral analysis

Sleep spindles

Spindles were detected at each electrode using a wavelet-based detector (Wamsley et al., 2012). The raw EEG signal was subjected to a time-frequency transformation using complex Morlet wavelets. Spindles were detected by applying a thresholding algorithm to the extracted wavelet scale in a range corresponding approximately 12 - 15Hz (center frequency 13.5Hz). A spindle was detected whenever the wavelet signal exceeded a threshold of nine times the median signal amplitude of artifact-free epochs for at least 400ms (Mylonas et al., 2019).

Slow oscillations

Slow oscillations were detected at each electrode during SWS using an automated algorithm. The data were band-pass filtered between 0.5 - 4Hz, and all positive-to-negative crossings were identified. Candidate slow oscillations were marked if two consecutive crossings fell 0.5 - 2 seconds apart. Peak-to-peak amplitudes for all candidate slow oscillations were determined, and oscillations in the higher 25th percentile (i.e. the 25% with the highest amplitudes) were retained and considered slow oscillations (Helfrich et al., 2018; Staresina et al., 2015).

Slow oscillation-spindle coupling

Coupling was calculated at every electrode in SWS. Data were band-pass filtered in the delta (0.5 - 4Hz) and sigma (12 - 15Hz) bands. The Hilbert transform was used to extract the instantaneous phase of the delta filtered signal and instantaneous amplitude of the sigma filtered

signal. For each detected spindle, the peak amplitude of that spindle was determined. Then, it was determined whether the spindle peak occurred within the time course of any detected slow oscillation. If a spindle was found to co-occur with a slow oscillation, the phase angle of the slow oscillation at the peak of the spindle was calculated. We extracted the percentage of all spindles coupled with a slow oscillation at each electrode, the average phase of the slow oscillation at the peak of each coupled spindle, and the overall coupling strength (mean vector length). Coupling phase was measured in degrees, with 0° being at the positive peak of the slow oscillation. Coupling strength was assessed using mean vector length measured on a scale of 0 - 1, where 0 indicates each coupled spindle occurred at a different phase of the slow oscillation, and 1 indicates that each coupled spindle occurred at the exact same slow oscillation phase.

Statistical analysis

Behavioral results have been reported in detail elsewhere (Kim et al., 2019). Briefly, memory was measured as corrected recognition (hit rate - false alarm) for each valence type. Positive and negative stimuli were averaged together to create a combined emotional memory corrected recognition score. ANOVAs and follow up t-tests were used as appropriate. High cortisol responders and low responders were then identified via a median split (see Kim et al, 2019 for details), resulting in n = 16 high responders and n =16 low responders.

Relationships between sleep oscillatory measures and memory were assessed via linear multiple regression models. For all analyses, we looked both at positive + negative averaged together (hereafter referred to as emotional memory) as well as positive and negative separately. All statistical analysis was performed in R (R Core Team, 2018). Between-group comparisons of correlation coefficients were performed using Fischer's r-to-z transformation (Fisher, 1925). Within-group comparisons were performed using Meng's z test (Meng et al., 1992). Both were carried out using the *cocor* package (Diedenhofen & Musch, 2015). For analyses of coupling, one participant from the stress group had their data excluded on the basis of being an outlier (>3SD from the mean).

Results

Behavior

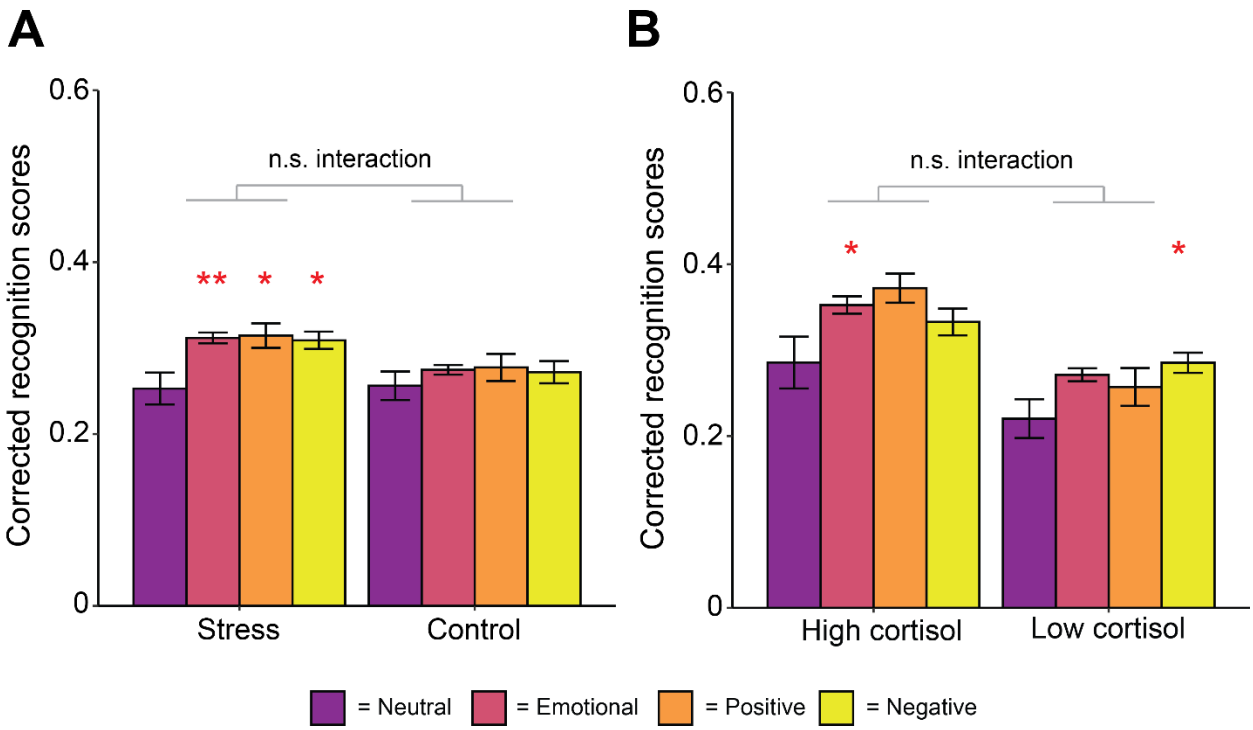

Figure 2. Behavior. Memory performance (hit rate – false alarm rate) for neutral, emotional (average of positive and negative), positive and negative items by **A** – stress condition and **B** – cortisol reactivity within the stress condition, as determined by a median split. Red asterisks represent significant differences compared to neutral items (** = p < .01, ** = p < .05). Errors bars represent the within-participant standard errors.

Although behavioral results, including efficacy of the TSST in evoking stress, are reported in our previous publication (Kim et al., 2019), we summarize them briefly here. Memory at the recognition test was significantly better for emotional compared to neutral items (t (63) = 2.67, p = .010), a pattern that was true for both negative (t (63) = 2.57, p = .013) and positive (t (63) = .2.28, p = .026) images. There was no difference between positive and negative items (t (63) = 0.38, p = .706).

To examine stress exposure on memory, corrected recognition scores were entered into a 2 (condition; stress, control) x 3 (image valence; negative, neutral, positive) mixed ANOVA. There was a significant effect of valence (F (2, 61) = 3.70, p = .030), whereby memory for neutral items was significantly lower than both positive and negative items (**Figure 2A**).

A similar analysis was run for high and low cortisol responders within the stress condition (**Figure 2B**). There was a significant main effect of valence (F (2, 29) = 3.85, p = .033), with neutral items being more poorly remembered than both positive and negative items. For both of these analyses, there surprisingly was no effect of stress condition/reactivity, nor were there any significant interactions.

Sleep

Group differences in sleep

Our previous report indicated no group differences in any measures of sleep macroarchitecture (Kim et al, 2019). As a first step, we examined whether there were any group differences in SWS spectral measures. This would test whether the stressor (or stress reactivity) itself impacted SWS oscillatory activity during the sleep period. Results are displayed in **Table 1**. There were no significant differences in any of the measures assessed.

Table 1. Group differences in SWS spectral measures

	Stress M (SD)	Control M (SD)	sig
Spindle density (spindles/min)	3.13 (1.78)	2.55 (1.08)	.12
Slow oscillation density (so/min)	6.58 (0.91)	6.98 (1.11)	.13
Slow oscillation amplitude (uV)	157.8 (26.25)	164.8 (34.28)	.37
% spindles coupled	15.69 (6.52)	16.14 (5.13)	.76
Coupling strength (vector length)	0.60 (0.15)	0.60 (0.15)	.92
Coupling phase angle (deg)	36.89 (18.60)	40.24 (14.12)	.42
	High cortisol responders M (SD)	Low cortisol responders M (SD)	sig
Spindle density (spindles/min)	3.53 (1.95)	2.74 (1.56)	.21
Slow oscillation density (so/min)	6.51 (0.58)	6.65 (1.18)	.69
Slow oscillation amplitude (uV)	164.5 (23.49)	151.1 (27.88)	.16
% spindles coupled	17.31 (7.69)	14.08 (4.81)	.17
Coupling strength (vector length)	0.58 (0.17)	0.63 (0.13)	.35
Coupling phase angle (deg)	34.85 (15.64)	38.92 (21.48)	.55

Note. M = mean, SD = standard deviation, sig = p value (uncorrected) from unpaired samples t-test, so = slow oscillation, deg = degrees. For coupling phase angle, 0 degrees represents the peak of the spindle occurred at the positive peak of the slow oscillation.

SWS time

There was a significant interaction between stress condition (TSST or control) and percentage of time spent in SWS for both neutral (β [95% CI] = 0.73 [0.04, 1.43], p = .044) and emotional (combined) (β [95% CI] = 0.79 [0.11, 1.48], p = .027) items (see **Supplementary Table 1** for full regression model output). The same pattern was seen when positive (β [95% CI] = 0.69 [0.002, 1.38], p = .054) and negative (β [95% CI] = 0.81 [0.12, 1.49], p = .025) items were examined separately. In the stress condition, a higher percentage of the sleep period spent in SWS was associated with better memory in all conditions (neutral, emotional, positive, and negative; all $r > .35$, all $p < .043$; **Figure 3**). However, this was not the case in the control group (all $r < -.16$, all $p > .40$). It should be noted that the overall regression models did not explain a significant proportion of the variance at the $p < 0.05$ level (**Supplementary Table 1**).

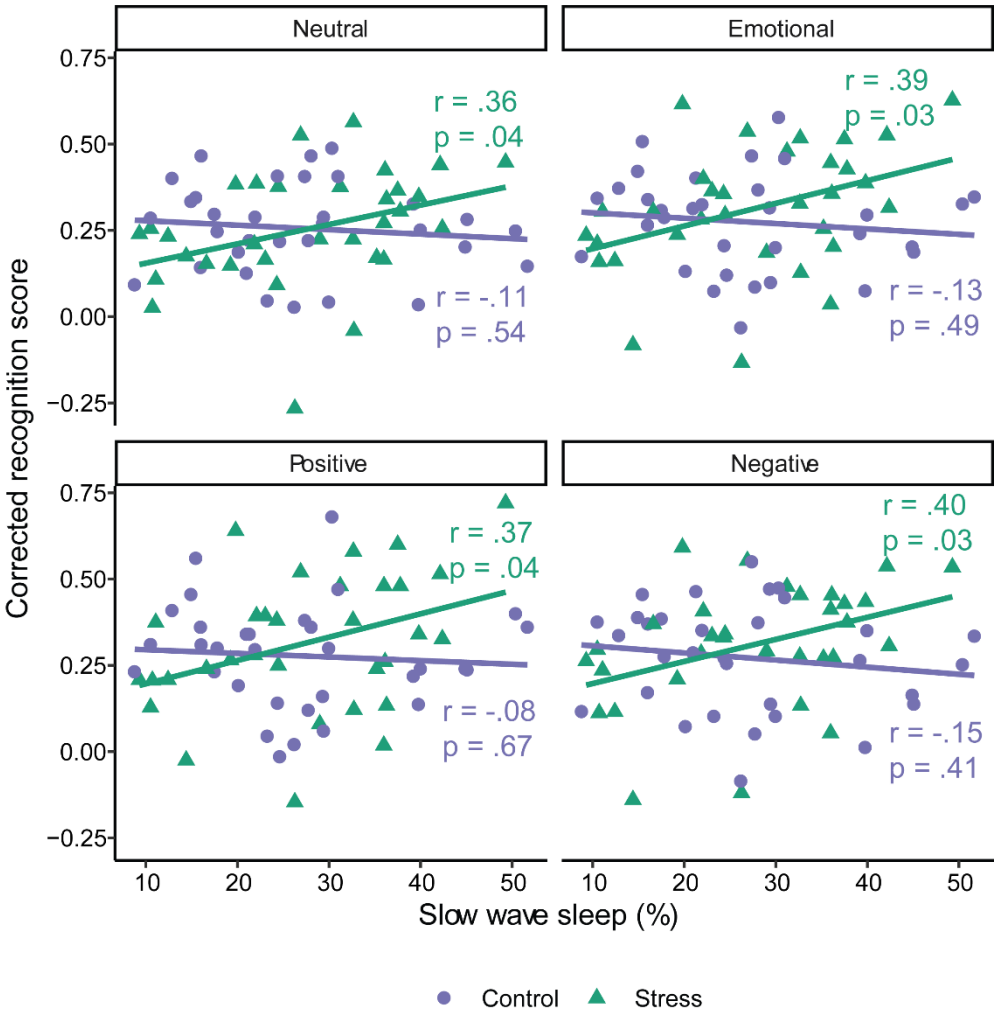

Figure 3. Associations between time spent in slow wave sleep and memory in the stress and control group. Emotional = Positive and negative item memory collapsed.

SWS time in high and low cortisol responders

We next explored whether the relationship between SWS time and memory in the stress group was driven by those who showed a high cortisol response following the stressor. There was no significant interaction between cortisol response and SWS time for any valence type (neutral: β [95% CI] = 0.26 [-0.71, 1.24], *p* = .60; emotional (combined): β [95% CI] = 0.49 [-0.43, 1.41], *p* = .30; positive: β [95% CI] = 0.37 [-0.53, 1.28], *p* = .43; negative: β [95% CI] = 0.59 [-0.37, 1.55], *p* = .24; **Figure 4; Supplementary Table 2**).

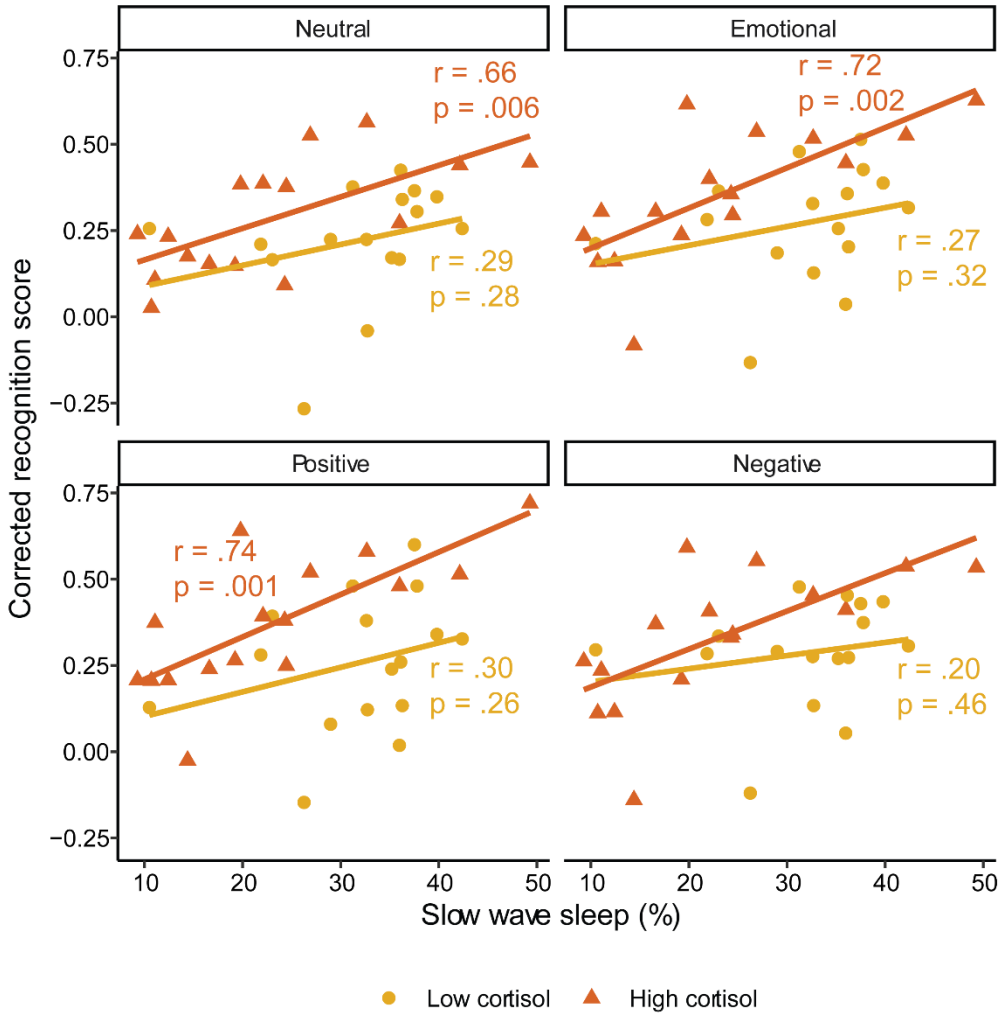

Figure 4. Associations between time spent in slow wave sleep and memory for high or low cortisol responders. Emotional = Positive and negative item memory collapsed.

Despite this, we note that correlations between SWS time and memory were only significant in the high responder group (neutral: $r = .66$, $p = .006$; emotional (combined): $r = .72$, $p = .002$; positive: $r = .74$, $p = .001$; negative: $r = .66$, $p = .005$). Correlations in the low responder group were all non-significant (all $r < .31$, $p > .25$). For all valence types, the between-group difference in correlation magnitude was not significant (all $z < 1.64$, $p > .09$).

Slow oscillation-spindle coupling

Next we investigated whether slow oscillation-spindle coupling during SWS was related to emotional memory consolidation following stress exposure. First, we examined the overall amount of coupling during SWS. As such, the percentage of all SWS spindles that co-occurred with a slow oscillation was used as the dependent variable. We took the average of frontal (F3, F4) and central (C3, C4) electrodes. Full regression model results are shown in **Supplementary Table 3**.

There was a significant interaction between slow oscillation-spindle coupling and stress condition (TSST or control) for neutral (β [95% CI] = -1.12 [-1.91, -0.33], $p = .007$) and emotional (combined) (β [95% CI] = -1.12 [-1.85, -0.40], $p = .003$) memory. In both cases, this was driven by a significant *negative* relationship in the stress group (neutral: $r = -.45$, $p = .01$; emotional (combined): $r = -.66$, $p < .001$), meaning that higher coupling was associated with *worse* memory performance following stress (**Figure 5**). Importantly, the correlation with emotional memory was significantly larger than for neutral memory ($z = 2.04$, $p = .04$), suggesting that coupling was more strongly related to impaired of emotional items compared to neutral. There were no significant relationships in the control group (neutral: $r = .19$, $p = .30$; emotional (combined): $r = -.08$, $p = .69$).

Significant interactions between coupling and stress condition were also found when positive (β [95% CI] = -1.08 [-1.80, -0.36], $p = .005$) and negative (β [95% CI] = -1.04 [-1.80, -0.28], $p = .01$) items were examined separately. In both cases, higher amount of coupling was associated with worse memory in the stress group (positive: $r = -.67$, $p < .001$; negative: $r = -.60$, $p < .001$),

whereas there was no relationship in the control group (positive: r = -.12, p = .50; negative: r = -.01, p = .94).

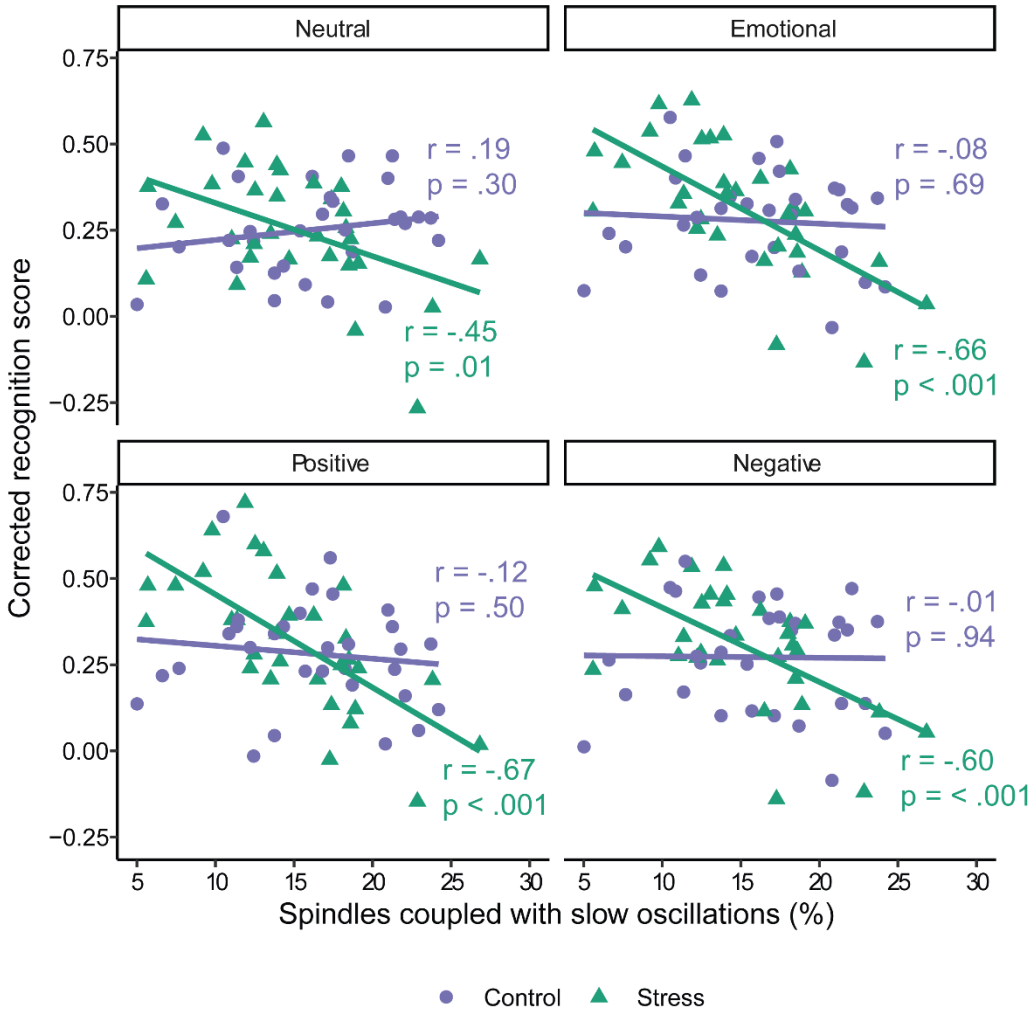

Figure 5. Associations between slow oscillation-spindle coupling and memory in the stress and control group. Coupling measures were averaged across frontal and central electrodes. Emotional = Positive and negative item memory collapsed

Coupling in high and low cortisol responders

Having found that slow oscillation-spindle coupling following stress is related to *worse* memory, we next sought to determine if the effect was driven by those who showed a high cortisol response to the stressor (**Figure 6**). Regression models did not indicate a significant interaction between coupling and cortisol response for any valence type (neutral: β [95% CI] = 0.34 [-0.74, 1.41], p = .55; emotional (combined): β [95% CI] = 0.15 [-0.76, 1.06], p = .75; positive: β [95% CI] = 0.13 [-0.75, 1.02], p = .77; negative: β [95% CI] = 0.16 [= -0.81, 1.13]; **Supplementary Table 4**).

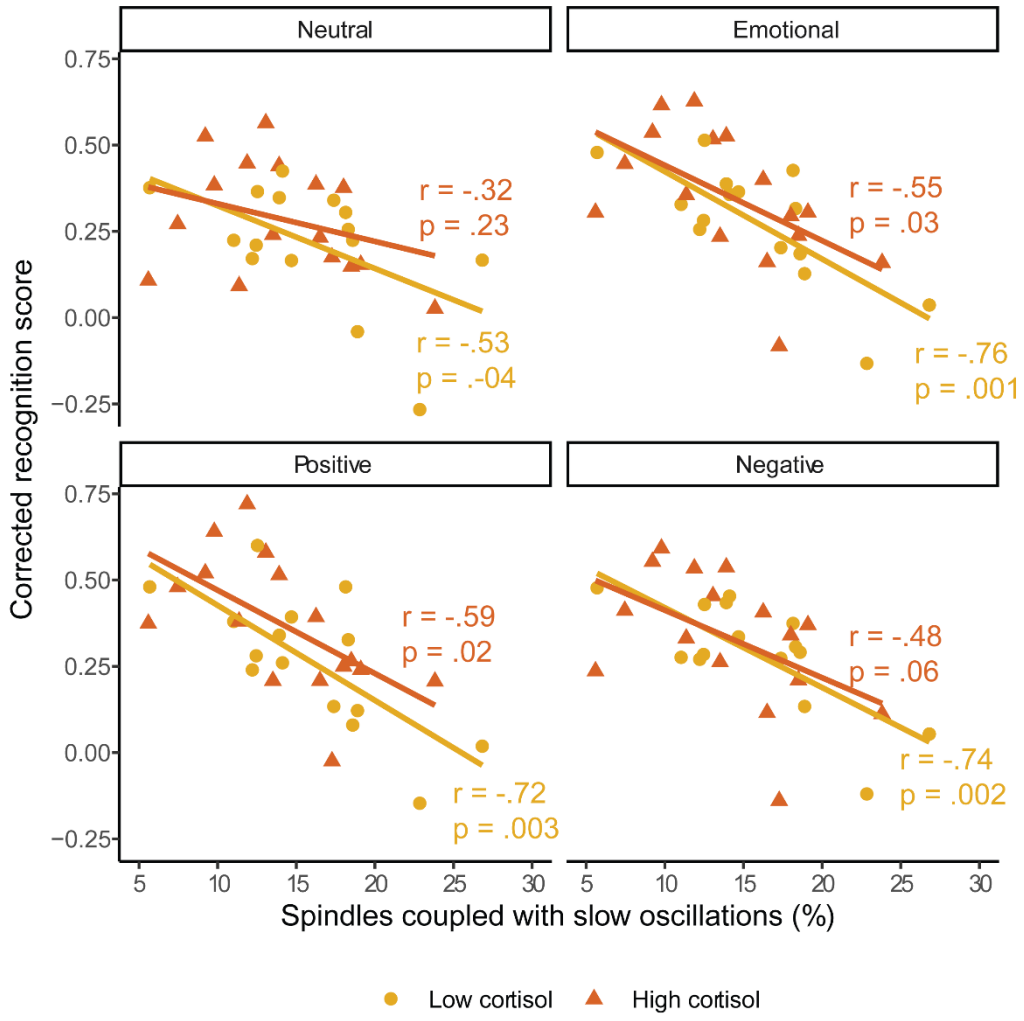

Figure 6. Associations between slow oscillation-spindle coupling in high and low cortisol responders. Coupling measures averaged across frontal and central electrodes. Emotional = Positive and negative item memory collapsed.

Coupling phase and strength

Having shown that the amount of coupling is associated with impaired memory following stress, we next evaluated whether the timing and/or consistency of coupling events were also implicated in this effect. With regards to both coupling timing and coupling strength, regression models for both neutral and emotional memory were non-significant (all $R^2 < .01$, all $p > .32$). Together, these analyses suggest it is the overall *amount* of slow oscillation-spindle coupling that is associated with worse emotional memory following stress, and this effect is not related to the consistency or phase timing of the coupling events themselves.

Discussion

We set out to explore the role of slow wave sleep (SWS) and slow oscillation-spindle coupling during SWS in facilitating sleep-stress interactions on emotional memory consolidation. Although recent theoretical and experimental evidence suggests a key role for SWS and slow oscillation-spindle coupling in memory consolidation (Klinzing et al., 2019), their role in *emotional* memory consolidation has yet to be explored, and possible interactions with stress are unknown.

First, we queried whether time spent in SWS correlates with memory for emotional, neutral, or both emotional and neutral items. A large body of research has linked consolidation of neutral episodic memories with time spent in SWS (Ackermann & Rasch, 2014; Plihal & Born, 1997), and more recently this has been extended to the consolidation of emotional memory as well (Alger et al., 2018; Payne et al., 2015). Studies that directly compare the benefit of SWS on neutral and emotional memory have found mixed results, with some reporting correlations with just emotional memory (Payne et al., 2015), or just neutral memory (Groch et al., 2015). In the present study, we found that time spent in SWS was positively associated with memory for both neutral and emotional items, but only in stressed participants. This suggests a more general memory function for SWS time such that, following stress at least, more time spent in SWS provides a memory benefit, but this benefit occurs for all items equally, independent of their emotional valence. SWS time may facilitate a sleep-stress interaction on memory, but this is not specific for emotionally valanced material.

Next, we looked at slow oscillation-spindle coupling events, which are believed to mediate consolidation (Klinzing et al., 2019; Rasch & Born, 2013). Contrary to our SWS time finding, the amount of slow oscillation-spindle coupling was *negatively* correlated with memory in the stress group. This suggests that coupling impairs memory following stress, rather than promote it as is typically found for non-stressed participants and neutral memories (Mikutta et al., 2019; Niknazar et al., 2015). These effects were stronger for emotional items compared to neutral ones, suggesting that stress and SWS coupling may interact to impede the consolidation of emotional memories to a greater extent than neutral memories. This inverse relationship underscores the importance of considering both broad sleep stages and specific neurophysiological events when investigating sleep's effect on memory. Following stress, it appears that sleep stage time and oscillatory events within that stage impact memory differently.

Future research is needed to fully understand why slow oscillation-spindle coupling negatively impacts emotional memory following stress. One possibility is that the nature of memory consolidation during SWS is not immediately suitable for highly salient memories formed under stress. Slow oscillation-spindle coupling is believed to facilitate systems consolidation during SWS, whereby hippocampal-dependent memories become more dependent on neocortical sites and are integrated into existing knowledge networks (Klinzing et al., 2019; Rasch & Born, 2013). This may not be appropriate for memories formed under stress where emotional tone is high. Over time, the affective response associated with a memory is diminished, leaving the experience itself with reduced emotional tone (Dolcos et al., 2005). It has been suggested that REM sleep could be involved in this process (Walker & van der Helm, 2009), and it is possible that more REM-based emotional processing is needed before a memory becomes fully integrated in the cortex via SWS-based consolidation. Under this hypothesis, consolidation of emotional memories in the stress group during SWS may be damaging because they are undergoing systems consolidation before other necessary offline processing is achieved. This could be tested in future studies whereby both sleep and memory are measured over longer time periods. In sleep immediately following learning, coupling would be expected to be negatively associated with emotional memory as found here. However, over longer time periods this may be reversed as the memory becomes ready to be integrated more into cortical networks.

The role of the amygdala in emotional memory formation and its activity during REM sleep have been well documented (Genzel et al., 2015; Murty et al., 2010). Far less is known however about amygdala activity during SWS in humans. Recent research has shown that sharp-wave ripples occur in the human amygdala during SWS, and these are temporally linked with both ripples in the hippocampus and sleep spindles (though notably not slow oscillations) (Cox et al., 2020). This provides a potential physiological basis for emotional memory consolidation during SWS, although an association with memory is yet to be reported. How amygdala-hippocampal interactions during SWS differ after stress is also unknown. As such, it remains possible that the negative association between coupling and emotional memory in the stress group could in part be driven by some currently uncharacterized process occurring between the hippocampus and the amygdala during SWS.

We found that stress alters the association between SWS and memory. It is notable that no associations between SWS activity and memory were found in the control group, given other research showing SWS-related benefits for both neutral and emotional episodic memory in non-stressed participants (Ackermann & Rasch, 2014; Cox et al., 2012; Denis et al., 2020; Groch et al., 2013; Mikutta et al., 2019; Niknazar et al., 2015; Payne, Stickgold, et al., 2008; Payne, Chambers, et al., 2012; Payne et al., 2015; Plihal & Born, 1997). While the reason for this finding is unclear, one possible explanation may be the delay interval used in this study design. In non-stressed participants, several studies have shown the benefit of sleep is largest if learning occurs close before sleep, with a sleep effect not being detected when there is a long wake period between learning and sleep. This has been demonstrated for both neutral (Denis et al., 2019; Gais et al., 2006; Payne, Tucker, et al., 2012; Talamini et al., 2008), and emotional memories (Payne, Chambers, et al., 2012). In the present study, participants left the lab and went about their day before returning to sleep. During that interval, memory strength may have deteriorated to the point to which sleep was unable to act on them. On the other hand, in the stress group, heightened cortisol during encoding could have led to stronger initial representations that were tagged for further offline processing (Shields et al., 2019), allowing later sleep to further strengthen and consolidate these memories.

The exploratory nature of this work means that it is important for future studies to replicate these findings with *a priori* hypotheses. Additional limitations should also be considered. Although emotional memory recognition was numerically higher in the stress group compared to the control group, we did not detect a significant interaction effect between stress and memory. This may suggest the study was underpowered to detect this group level interaction, and future research should work to employ larger sample sizes. This study also lacked a wake control group. As such, it is not possible to say that sleep led to a significant emotional memory benefit compared to time spent awake. This sleep-specific benefit, however, has been frequently documented in prior research (Payne, Stickgold, et al., 2008; Payne & Kensinger, 2010; though see Lipinska et al., 2019; Schäfer et al., 2020). Additionally, this does not preclude correlational analyses between memory and sleep neurophysiology, the primary focus of this investigation.

Notably, we did not find any differences in SWS oscillatory events between the stress and control groups. This differs from previous research, which has found that psychosocial stress

impacts the architecture of subsequent sleep, in particular reducing SWS time and reducing slow wave (0.5Hz-4.5Hz) oscillatory power (Ackermann et al., 2019; Kim & Dimsdale, 2007). There are several possible reasons for this discrepancy. First, previous work showing changes in slow wave power following stress were looking at changes within an afternoon nap that occurred in close proximity to the stressor, rather than overnight sleep (Ackermann et al., 2019). Cortisol levels around the time of sleep onset and the sleep period itself may have been higher in the Ackermann et al. study than in ours which led to the alterations in spectral activity (Ackermann et al., 2019). The natural circadian rhythm of cortisol means that cortisol levels around sleep onset in our overnight design (~11pm) would most likely be lower than at sleep onset in an afternoon nap. In addition, approximately 9 hours elapsed in our study between the stressor and sleep onset, as opposed to ~3 hours in the Ackermann et al study. Previous work has examined spectral power in a wide frequency range of 0.5-4.5Hz, which includes both slow oscillation and delta frequency activity. It is possible that stress leads to elevation in overall spectral power in this band without impacting the individually detected slow oscillatory events. Finally, Ackermann et al. noted that changes in sleep following stress were not seen across the whole nap period, but only in the first 15 minutes. How this time-dependent in effect in a nap would map to a full night of sleep is unclear but is worthy of future investigation.

More generally, our findings demonstrate the importance of not relying solely on sleep stage correlations when probing sleep and memory associations (Lim et al., 2020; Muehlroth & Werkle-Bergner, 2020; Simor et al., 2020). By simply assessing time spent in SWS, no consideration is given to specific neurophysiological events. It is equally important to also examine the specific oscillatory events that occur during different periods of sleep. Recent experimental work has emphasized a mechanistic role for discreet events occurring during SWS that underpin memory consolidation processes (Klinzing et al., 2019; Latchoumane et al., 2017). To this end, coupling between slow oscillations, sleep spindles, and sharp-wave ripples mediate the consolidation of memories during sleep (Latchoumane et al., 2017). Furthermore, as we show here, these macro and micro level features of sleep can in fact have opposite effects on memory, and show selective effects based on memory valence and stress around the time of initial encoding.

In summary, this study adds to a small but growing body of research examining interactions between sleep and stress in the processing of emotional memories. We examined, for the first time, the role of key SWS oscillations in this process. To our surprise, we found that increased coupling between slow oscillations and sleep spindles impaired emotional memory following stress. Future research should seek to replicate this finding, and further probe the possibility that stress leads to a change in the function of slow oscillations and their coupling with spindles. If confirmed, this would have important implications for understand how sleep and stress facilitate long-term emotional memory.

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